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INTRODUCTION TO ORGANIC
AND
BIOLOGICAL CHEMISTRY

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AND
BIOLOGICAL CHEMISTRY

by

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SECOND EDITION

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To

ROSS AIKEN GORTNER

Whose inspirational leadership,
contagious enthusiasm, and warm,
personal friendship endeared him
to student and associate alike

PREFACE TO SECOND EDITION

The kindly reception accorded the First Edition has confirmed our original impression that a text of this type would be useful. This cordial reception and the many advances in organic and biological chemistry during the past five years have prompted us to prepare a second edition.

While the order of presentation and purposes of the first edition have been retained in the present revision, many sections have been rewritten to include new material or to secure better logic and clarity. In addition, we have deemed it necessary to add a number of new sections in order to incorporate some of the unprecedented developments that have occurred during the past five years as a result of wartime research. Some of the new sections added are those on antimalarials, fluorine compounds, silicones, mercaptans, penicillin, and the microbiological assay of amino acids.

In order to incorporate recent significant developments, it was necessary to rewrite and enlarge the sections on petroleum, the chemical structure of starch, and the structure of pectin. Other sections which have been revised extensively and in which new material has been added, include synthetic rubbers, plastics, industrial uses of proteins, nylon, sulfa drugs, curare, and the D-L nomenclature. Whenever it has been necessary to discuss a controversial subject, we have made an honest effort to present the current point of view of the majority of the competent investigators in the field.

An effort has been made to delete obsolete material, and condensation has been effected, where possible, in order not to increase unnecessarily the size of the book.

The policy of emphasizing material of interest and use to students in premedical, predental, agricultural, home economics, and dietetics courses has been retained in this edition.

Nothing is so helpful or stimulating to an author as the criticisms and suggestions of teachers and students who use his book. We are most grateful to those who have sent us their comments. They have been very useful to us in preparing this second edition. Errors pointed out to us have been corrected; possibly others remain. We would appreciate further criticisms and suggestions. These will aid, we hope, in increasing the usefulness of the book.

We acknowledge with deep appreciation the able assistance of Mrs. Lois L. Reitz, Miss Maureen Wade, and Mrs. Evelyn Zerfing, who typed the material for the new edition. We are grateful to Mrs. Jennie M. Arnow for her aid in revising the index.

L. EARLE ARNOW
HENRY C. REITZ

PREFACE TO FIRST EDITION

This book has been written because we believe there is a definite need for it. Excellent elementary textbooks of organic chemistry and of biochemistry are available, but no other single brief volume, covering both these fields, is known to us. We have endeavored to include material that will be both useful and interesting to students in premedical, predental, home economics, agriculture, dietetics, and physical education courses, as well as to others who may be interested in the correlation of chemistry with biological sciences.

Part I is a review of chemical fundamentals. It has been found that such a brief review often is helpful to students who are beginning their study of organic and biological chemistry. It is not expected that it will be necessary for the instructor to use class time to consider the material dealt with in Part I other than, perhaps, to assign it, and possibly to answer a few questions that may arise in the mind of the student after he has made an independent study of the chapters.

Part II deals with the subject matter of organic chemistry. Experience with a large number of students has shown that one of the principal reasons some students find the subject matter of organic chemistry to be difficult is that they fail to use correct methods of study. It is for this reason that suggestions of technics and methods for successful study have been included before the subject matter of Part II is presented. Every effort has been made to relate, in so far as possible, the study of organic chemistry to the everyday life of the student. Uses of organic compounds are stressed, and, in addition, the interrelationships of organic chemistry with the manufacture of many products with which the student is familiar are considered. Such topics of timely interest as synthetic rubber, plastic materials, explosives and new textile fibers are discussed in connection with the organic compounds to which they are related. The topic of petroleum is presented in greater detail than is customary in most organic chemistry textbooks, because it is felt that the ever-increasing number of products that are manufactured from this basic raw material warrants such a treatment.

Part III is a summary of the more important phases of metabolism and nutrition. The digestion, intermediary metabolism, and excretion of each of the major types of biological compounds (carbohydrates, lipids, proteins) have been treated as a unit; that is, we have followed a chemical, rather than the more usual physiological or anatomical, outline in preparing this section. This method of presentation has enabled us to save considerable space without, we believe, omitting essential material. Special chapters on digestion, absorption, blood, and excretion were made unnecessary.

Selected references have been included at the end of most of the chapters. It is hoped that these will serve as an aid to those who are interested in securing more detailed information about the various topics discussed. Many key articles and review papers selected contain long bibliographies that will assist the interested person in familiarizing himself with the original work in the particular field. An attempt has been made to include recent, pertinent articles, except where it was deemed necessary to refer to older articles in order to give background and understanding for later developments. Standard textbooks, as well as advanced treatises and monographs, have been listed: they contain valuable discussions of topics that the limitations of space make impossible in this book.

We wish to express our thanks to Dr. Richard H. Barnes, Dr. Leo T. Samuels, and Mr. and Mrs. John Brecher, who have read and criticized constructively portions of the manuscript. Deep appreciation is due to Professor R. A. Gortner and Professor C. H. Bailey for suggestions and assistance in preparing outlines of courses taught by one of us (H. C. R.) upon which much of the material in Part II is based. We wish to thank Mrs. Lois L. Reitz for her assistance in typing a major portion of the manuscript. Lastly, we are grateful to Mrs. Jennie M. Arnow and Mrs. Sallie W. Martin for their aid in preparing the index.

L. EARLE ARNOW
HENRY C. REITZ

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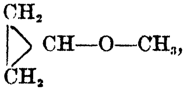
Methyl Ether, $CH_3—O—CH_3$, 173; Ethyl Ether, $C_2H_5—O—C_2H_5$, 173; Cyclopropylmethyl Ether,  $\left.\begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\right\rangle CH—O—CH_3$, 176; Isopropyl Ether, $(CH_3)_2CH—O—HC(CH_3)_2$, 176; Dichlorodiethyl Ether, $ClCH_2CH_2—O—CH_2CH_2Cl$, 177; Thio Ethers, 177; Oxides, 178; Dioxane, 179; Study Questions, 180.

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PART I

CHEMICAL FUNDAMENTALS IN REVIEW

CHAPTER I

CHEMICAL FACTS AND THEORIES

Introduction.—Chemistry is a science that concerns itself with all the countless materials of which our universe is made. The chemist is interested in the composition of these materials, in the changes in composition which they undergo, and in the underlying mechanisms by means of which these changes are accomplished. Modern civilization, as we know it, would not be a reality if many thousands of chemists, working in thousands of laboratories, had not learned to direct some of these changes, and, by means of them, to create new and useful things.

Elements and Compounds.—Scientists have learned that everything occupying space and having mass (weight) is composed of one or more simple substances. These simple substances, which cannot be made simpler by any sort of chemical procedure, are called *elements*. The elements known to exist in nature are listed on page 749.

The new substance formed whenever two or more of these elements combine, or unite chemically with each other, is called a *compound*. It has been estimated that more than 500,000 compounds have been prepared and studied. Compounds often differ greatly in their chemical and physical properties from the elements of which they are composed. For example, when the elements iron and oxygen combine chemically with each other, iron rust (ferric oxide) is formed. Iron is a silvery metal and oxygen is a colorless gas; the rust which results from their union is a red-brown, crumbly solid.

Chemical Changes.—A *chemical change* is said to occur whenever a change in chemical composition takes place. The formation of rust is an example of such a change. The union of elements to form a compound, the breaking down of a compound to form elements, and the formation of new compounds by reactions involving other compounds or elements are all chemical changes. In contrast to physical changes (such as the melting of ice or the movement of wind), chemical changes cannot be reversed except by altering the composition of the substances formed as a result of the change.

Catalysts.—The speed with which a chemical reaction (change) takes place often can be accelerated or slowed by the addition of a suitable substance, called a *catalyst,* to the reacting materials. Catalysts themselves are not permanently altered by the reaction, and do not influence the compositions of the new substances formed; they merely cause them to be produced faster or slower, as the case may be. Most of the important chemical changes that take place in our tissues would be slow indeed if nature had not provided us with efficient catalysts known as enzymes. Some types of stainless steel contain small amounts of the catalysts nickel and copper. The presence of these two elements causes the union of the iron in the steel with the oxygen of the air to proceed so slowly that no appreciable formation of rust can be observed even after many years.

The Atomic Theory.—The atomic theory, first stated early in the last century by the Englishman John Dalton, is accepted by all modern chemists. According to this theory, all elements are composed of tiny, discrete particles called *atoms.* Some of the more important properties of atoms are listed below:

1. The atoms of any one element are different in weight and in chemical properties from the atoms of all other elements.

2. Each of the atoms of any one element undergoes exactly the same types of chemical reaction as do other atoms of the same element.

3. The individual atoms of a single element may vary, usually only slightly, in weight. Thus, an uncommon type of carbon atom weighs thirteen-twelfths as much as the more abundant type. However, the *average* weight of the atoms of an element is always the same for all natural samples of the element.

4. Atoms are in constant motion. The speed of this motion depends on the temperature; it increases when the temperature is raised, and decreases when the temperature falls. Theoretically, all linear motion of atoms should cease at a temperature of approximately –273° C. (absolute zero). Scientists have not yet succeeded in reaching the absolute zero, although temperatures only a fraction of a degree above it have been attained.

5. Under proper conditions most atoms have the ability to combine firmly with one or more other atoms. The new particles formed by such unions are called *molecules.* A molecule, then, is the smallest single particle of a compound. A sample of the compound water is made up of billions of molecules, each of which contains two hydrogen atoms and one oxygen atom firmly united together.

6. Only whole atoms can take part in chemical reactions.

Atomic and Molecular Weights.—Chemists have found it convenient to adopt a scheme of relative weights of atoms. Oxygen, which has been assigned an *atomic weight* of 16, is the standard element for the determination of these weights. For example, the atomic weight of helium is 4, because the average weight of an atom of helium is only one-fourth that of an oxygen atom. Since, on the average, a sulfur atom weighs twice as much as an oxygen atom, the atomic weight of sulfur is 32. A complete table of atomic weights will be found on page 749.

Molecular weights are calculated by finding the sum of the atomic weights of each of the atoms combined in a molecule. The sulfur dioxide molecule contains one sulfur atom and two oxygen atoms. Since the atomic weight of sulfur is 32, and that of oxygen is 16, the molecular weight of sulfur dioxide is 64 $(32 + 16 + 16)$.

Atomic weights of elements, expressed in grams, are called *gram-atomic weights.* Molecular weights of compounds, expressed in grams, are called *gram-molecular weights, gram moles, or moles.* Thus, 16 g. of oxygen is a gram-atomic weight of this element, and 64 g. of sulfur dioxide is a gram-molecular weight (mole) of this compound.

An important law (Avogadro's law) states that gram-atomic weights, or gram-molecular weights, of chemical substances contain the same number (6.06×10^{23}) of atoms or molecules, as the case may be. We have learned already that a molecule of sulfur dioxide is four times as heavy as an atom of oxygen. Avogadro's law merely tells us that 6.06×10^{23} molecules of sulfur dioxide weigh four times as much as 6.06×10^{23} oxygen atoms. Stated in a different manner, the low predicts that 64 g. of sulfur dioxide (one gram-molecular weight) will have the same number of molecules as there are atoms in 16 g. of oxygen (one gram-atomic weight), since the ratio of weights is 4 to 1.

The Supposed Structure of the Atom.—All atoms are believed to be composed of exceedingly tiny particles of matter, called subatomic particles. Some of these particles have a negative electrical charge, some are electrically neutral (i.e., have no charge), and some are positively charged. The subatomic particles that have been postulated are given in Table I.

TABLE I

SUBATOMIC PARTICLES

	POSITIVE CHARGE	NEGATIVE CHARGE	NO CHARGE
Heavy	Proton	(Negative proton)*	Neutron
Intermediate	Positive meson	Negative meson	(Neutral meson)*
Light	Positron	Electron	(Neutrino) †

*Particles in parentheses have not been *proved* to exist.

†Some scientists think of the neutrino (not yet proved to exist) as a particle of energy rather than of mass.

It is probable that most, if not all, stable atoms are made of electrons, protons, and neutrons. The other types of particle most likely are formed only when atoms are disintegrated (i.e., torn apart) by a suitable procedure, such as bombarding them with a stream of neutrons. Practically the entire weight of an atom is due to its protons and neutrons, since each of these particles weighs about 1,800 times as much as an electron.

The atomic protons and neutrons are located somewhere near the center of the atom, in a region called the *nucleus*. Revolving around this nucleus in concentric orbits are the electrons. Sometimes they are called *planetary electrons,* because they revolve around the nucleus much as the planets revolve around the sun. The electrons are not scattered indiscriminately about the nucleus; instead, they are located in definite orbits. The first orbit, that is, the one closest to the nucleus, can contain no more than 2 electrons. The second orbit is filled when it contains 8 electrons. The number of electrons that can exist in the remaining orbits is more variable and complicated, and we need not concern ourselves with them.

If the 92 elements are arranged in the order of their atomic weights, it is possible to assign each of them a number, called the *atomic number.* The lightest element, hydrogen, has an atomic number 1; uranium, the heaviest natural element, has an atomic number 92. We believe today that the atomic number has a fundamental significance: *it indicates the number of planetary electrons present in the atom.* For example, when we learn that the atomic number of oxygen is 8 (see page 749), we know at once that the oxygen atom has 8 planetary electrons. Since the first electron shell (orbit) can hold only 2 electrons, 6 of the 8 electrons of oxygen must be in the second shell. Now, under ordinary circumstances, atoms are electrically neutral; that is, they possess equal numbers of positive and negative electrical charges. It follows, then, that the nucleus of the oxygen atom must have a charge of 8+, because 8 negative charges are carried by the 8 planetary electrons (each electron has a charge of 1–). With these facts in mind, it becomes possible to draw a diagram of the oxygen atom (see Fig. 1).

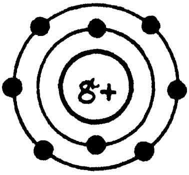


Fig. 1.—Diagram illustrating the supposed structure of the oxygen atom. How many neutrons are thought to be present in the nucleus of this atom?

The atomic weight of oxygen is 16. We interpret this to mean that the nucleus of an oxygen atom contains 16 "heavy" subatomic particles. Eight of these particles are protons. This accounts for the nuclear charge of 8+, since each proton has a charge of 1+. The other 8 particles are thought to be neutrons, which have no electrical charge.

Sodium has an atomic weight of 23 (approximately) and an atomic number of 11. The sodium atom, then, must have 11 planetary electrons (2 in the first shell, 8 in the second shell, and 1 in the third shell). Its nucleus contains 11 protons; hence its nuclear charge must be 11+. If we remember that the sum of the protons and neutrons in the nucleus must equal the atomic weight, it becomes clear that the sodium nucleus contains 12 neutrons. A diagram of the sodium atom is shown in Fig. 2.

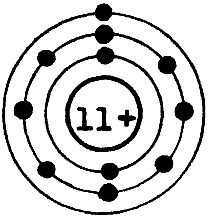


Fig. 2.—Diagram illustrating the supposed structure of the sodium atom. How many protons are thought to be present in the nucleus of this atom?

Isotopes.—The atomic weight of chlorine is 35.46. How many "heavy" subatomic particles are we to suppose are present in the nucleus of the chlorine atom? Are 36 such particles present, or are there only 35? It has been found that two different kinds of chlorine atom exist. Both kinds have 17 planetary electrons and 17 protons in the nucleus. Both have nearly identical chemical properties. However, one kind has 18 neutrons in its nucleus; the other type has 20. The atomic weight of the light chlorine atom is 35 (17 protons and 18 neutrons); the heavy atom has an atomic weight of 37 (17 protons and 20 neutrons). The figure, 35.46, therefore indicates the *average* number of "heavy" subatomic particles present in the atoms contained in a sample of chlorine. These two forms of chlorine are called *isotopes.* Probably all elements exist in the form of isotopes. Fundamentally, isotopes differ from each other in one way only: the nuclei of their atoms contain slightly different numbers of neutrons.

Atomic Energy.—The nucleus of an atom, under ordinary circumstances, probably contains only protons and neutrons (see page 24). Since the protons are positively charged, and since like electrical charges repel each other, it will be apparent that an enormous amount of energy would be required to bring protons as close to each other as they must be in an atomic nucleus. If it is remembered that energy cannot be destroyed, it is evident that this vast store of energy would be released if the protons were separated from each other—that is, if the nucleus of the atom were broken up into the individual subatomic particles of which it is made. It can be calculated that 1 g. of helium, one of the lightest elements, contains sufficient nuclear energy to run an ordinary 100-watt light bulb for about 30,000 years. In recent years it has been found possible to cause the nuclei of some of the heaviest atoms to split, thus releasing a portion of the nuclear energy contained within them. One method of doing this is to bombard an isotope (see page 26) of uranium, known as uranium 235 (or, U235) because its atomic weight is 235, with neutrons. When the neutrons strike U235 nuclei, the nuclei are broken into smaller pieces and energy is released. This nuclear ''explosion'' also causes the release of more neutrons, and these can then cause other U235 nuclei to ''explode.'' Under ideal conditions, this results in what is known as a chain reaction; that is, the process continues automatically until collisions of neutrons and nuclei no longer occur with sufficient frequency to allow the process to go on. In order for a chain reaction to occur, the mass of U235 must be sufficiently great so that the neutrons produced cannot escape without striking a nucleus. Probably the atomic bomb used in the recent war contained two or more pieces of U235 of insufficient mass to allow a chain reaction to occur. At the time of explosion, presumably these masses were brought together to make one large mass, which then exploded as a result of the chain reaction.

Four new elements, all heavier than uranium (the heaviest naturally occurring element), have been made in the laboratory as the result of studies of nuclear energy and nuclear splitting. They have been named neptunium (atomic number 93, atomic symbol Np), plutonium (atomic number 94, atomic symbol Pu), americium (atomic number 95, atomic symbol Am), and curium (atomic number 96, atomic symbol Cm). Plutonium has been found to be even more useful for the production of nuclear explosions than is U235.

Atomic and Molecular Symbols.—Chemists have developed a shorthand of their own. Each element has been given a symbol consisting of one or two (but never more) letters. If the atomic symbol contains two letters, the first letter is capitalized, but the second one is not. If the symbol is one letter only, it is always capitalized. Some illustrative atomic symbols are given in Table II. A complete list of them will be found on page 749.

TABLE II

SYMBOLS AND VALENCES OF SOME ELEMENTS

NAME	SYMBOL	USUAL VALENCE
Metals		
Aluminum	Al	3+
Barium	Ba	2+
Calcium	Ca	2+
Copper	Cu	1+ or 2+
Iron	Fe	2+ or 3+
Lead	Pb	2+
Magnesium	Mg	2+
Mercury	Hg	1+ or 2+
Potassium	K	1+
Silver	Ag	1+
Sodium	Na	1+
Zinc	Zn	2+
Non-metals		
Bromine	Br	1−
Chlorine	Cl	1−
Fluorine	F	1−
Hydrogen	H	1+
Iodine	I	1−
Oxygen	O	2−
Sulfur	S	2−, 4+, or 6+

Some of the atomic symbols are derived from the Latin names of the elements. For example, the Latin name for iron is *ferrum;* for mercury, *hydrargyrum;* and for silver, *argentum.*

The atomic symbol is more than a mere abbreviation for the element. Ca means calcium, but it means also *1 atom of calcium,* or *1 gram-atomic weight of calcium.* Three atoms of iron, or 3 gram-atomic weights of iron, may be indicated with the shorthand expression, 3 Fe. Notice that whenever we wish to indicate only 1 atom, the figure 1 is not written. *The figure 1 is never written in chemical shorthand.*

The symbols for molecules are written as suitable combinations of atomic symbols. The number of any one type of atom present in one molecule is indicated by writing a small subscript number *after* the atomic symbol. A molecule of cane sugar contains 12 carbon atoms, 22 hydrogen atoms, and 11 oxygen atoms. Therefore, the formula for "1 molecule of cane sugar" is $C_{12}H_{22}O_{11}$. If we wish to indicate 5 molecules, or 5 gram moles, of cane sugar, we use the symbol, $5\ C_{12}H_{22}O_{11}$. The abbreviation for "10 molecules of water" or for "10 gram moles of water" is $10\ H_2O$. The molecular formula H_2O tells us that each molecule of water contains 2 hydrogen atoms and 1 oxygen atom.

The Chemical Equation.—The chemical equation is used as a shorthand method of describing what happens when chemical substances react to form new substances. Suppose we write an equation for the reaction between silver fluoride (AgF) and barium chloride ($BaCl_2$) to form barium fluoride (BaF_2) and silver chloride ($AgCl$):

Step 1. First, we write down the formulas (molecular symbols) for silver fluoride and for barium chloride, separating them by means of a + sign.

$$AgF + BaCl_2 \rightarrow$$

Since we do not yet know how many molecules (or gram moles) of each compound will be required for the reaction, we start with only 1 molecule (or gram mole) of each. The arrow is used to separate the reacting molecules from the new substances formed by the reaction (see Fig. 3, *a* and *b*).

Step 2. On the right of the arrow, we write the formulas for the new substances formed by the reaction (see Fig. 3 *c*).

$$AgF + BaCl_2 \rightarrow BaF_2 + AgCl$$

Step 3. An important law, known as the *law of conservation of matter,* tells us that atoms can neither be created nor destroyed by chemical reactions; that is, the *number and kind* of atoms must be the same both in the reacting compounds and in the new products formed. In other words, there must be the same number and kinds of atoms on both sides of the arrow. As our third step, then, we must *balance the equation.* Inspection of the equation, as it now stands, shows us that only 1 fluorine atom is on the left of the arrow; 2 fluorine atoms are on the right. Since each molecule of silver fluoride contains only 1 fluorine atom, it becomes apparent that the above reaction cannot take place unless 2 molecules of silver fluoride are present. Accordingly, we modify the equation to read (see Fig. 3 *d*):

$$2\ AgF + BaCl_2 \rightarrow BaF_2 + AgCl$$

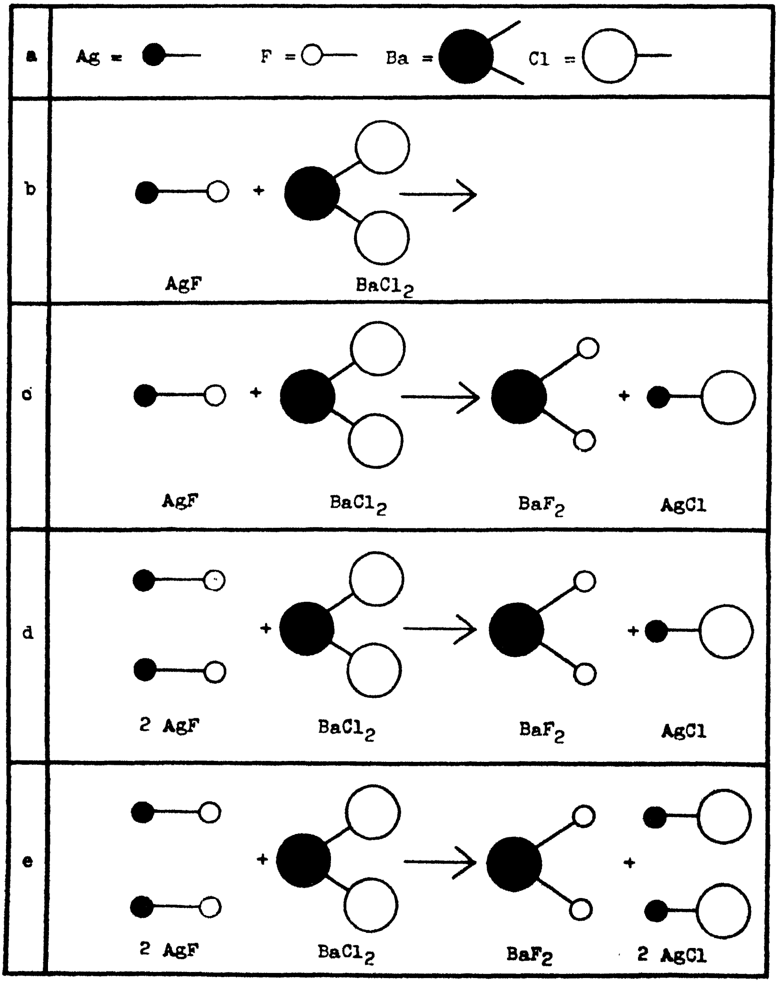


Fig. 3.—Diagram illustrating the steps employed in writing and balancing a chemical equation. Why must the equation be balanced?

This takes care of the fluorine, but further inspection shows us that, whereas 2 silver atoms are indicated on the left of the arrow, only 1 of them is shown on the right. Obviously, 2 molecules of silver chloride must be formed by the reaction; in no other way could 2 silver atoms be present when the reaction is completed. If we indicate this (Fig. 3 *e*), the equation reads:

$$2\ AgF + BaCl_2 \rightarrow BaF_2 + 2\ AgCl$$

Since the number and kinds of atoms are now the same on both sides of the arrow, the equation is completed. It tells us that 2 gram moles of silver fluoride (325.82 g.) will react with 1 gram mole of barium chloride (208.27 g.) to form 1 gram mole of barium fluoride (175.36 g.) and 2 gram moles of silver chloride (286.68 g.).

Radicals.—Sometimes groups of atoms tend to cling together and to act in chemical reactions as though they were really only one atom. Such groups of atoms are called *radicals*. The reaction between sodium carbonate and calcium chloride may be written as follows:

Na_2CO_3	+	$CaCl_2$	→	2 $NaCl$	+	$CaCO_3$
Sodium carbonate		Calcium chloride		Sodium chloride		Calcium carbonate

Here the CO_3 group of atoms (the carbonate radical) has traded sodium atoms for a calcium atom. Some typical radicals are listed in Table III.

Valence.—When we examine the formulas for the following compounds, it becomes evident that different atoms have different abilities to combine with other atoms.

HCl	H_2O	NH_3	CH_4
Hydrochloric acid	Water	Ammonia	Methane

One atom of chlorine (Cl) can combine with only 1 atom of hydrogen (H); an oxygen (O) atom can combine with 2 hydrogen atoms; a nitrogen atom (N) can unite with 3 such atoms; and a carbon atom (C) can unite with 4 hydrogen atoms. If an element will combine chemically with hydrogen, *the number of hydrogen atoms that will unite with 1 atom of the element* *is called the valence of the element.* If an element will not combine with hydrogen, its valence must be found by analogy. For instance, the formula for sodium chloride is NaCl. Sodium ordinarily will not combine with hydrogen. However, since 1 atom of either hydrogen or sodium can combine with only 1 atom of chlorine, we reason that both sodium and hydrogen have the same valence. Since the valence of hydrogen is 1, the valence of sodium also must be 1.

Hydrogen and the elements or radicals that will not combine with hydrogen are said to have *positive* valence; other elements and radicals are said to have *negative* valence. When an element is not combined with any other element, we say it has zero valence. For example, the oxygen of the air has zero valence, but, when oxygen combines with hydrogen to form water, its valence becomes 2–. The valences of some important elements and radicals are listed in Tables II and III.

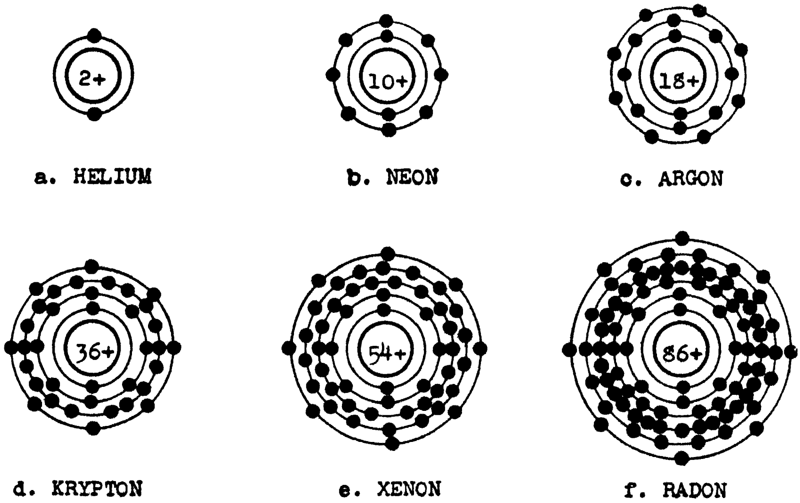
TABLE III

SYMBOLS AND VALENCES OF SOME RADICALS

NAME	SYMBOL	VALENCE
Ammonium	NH_4	1+
Bicarbonate	HCO_3	1–
Carbonate	CO_3	2–
Hydroxyl	OH	1–
Nitrate	NO_3	1–
Nitrite	NO_2	1–
Phosphate	PO_4	3–
Sulfate	SO_4	2–
Sulfite	SO_3	2–

Elements or radicals with positive valence will combine only with elements or radicals that have negative valence. In every molecule *there must be an equal number of positive and negative valences.*

Certain elements, known as the rare gases, are so stable chemically that they will not combine with other elements to form compounds. Diagrams of the atoms of these elements are shown in Fig. 4. Notice that all of them, except helium, have 8 electrons in the outer electron shell. (Even in the case of helium, the outer shell is filled; remember that the first shell can contain only 2 electrons.) This leads us to suppose that *atoms are most stable when their outer shells contain 8 electrons.* Fig. 5 illustrates what happens when a sodium atom combines with a chlorine atom to form a molecule of sodium chloride. The sodium atom, which has only 1 electron in its outer shell, gives this electron away, and thus arranges itself so that its new outer shell contains 8 electrons. The chlorine atom, which has only 7 electrons in its outer shell, takes the electron from the sodium atom, and thus fills its outer shell. Since sodium has *lost* one negative charge (an electron), it is said to have a valence of 1+; chlorine, which has *gained* one negative charge, is said to have a valence of 1–. Opposite charges of electricity attract one another; the positively charged sodium atom and the negatively charged chlorine atom attract each other and unite, or stick together, to form the sodium chloride molecule. This type of valence, in which atoms actually gain or lose electrons, is called *electrovalence.*



a. HELIUM b. NEON c. ARGON

d. KRYPTON e. XENON f. RADON

Fig. 4.—Diagrams illustrating the supposed atomic structures of the rare gases. What is the valence of one of these gases?

In some cases, when atoms combine they do not give away or receive electrons; instead, they merely share electrons with each other. This type of valence, called *covalence,* is illustrated in Fig. 6. Notice that each hydrogen atom shares its single electron with the oxygen atom. In turn, the oxygen atom shares 1 of its 6 outer electrons with each of the 2 hydrogen atoms. As a result of this cooperation each atom succeeds in filling its outer shell.

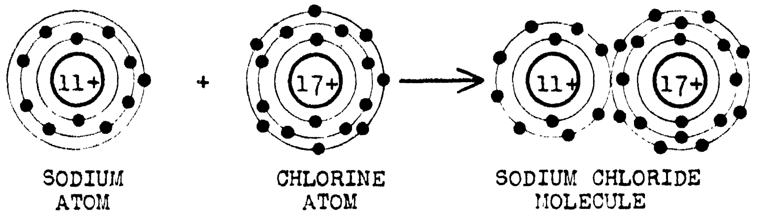


Fig. 5.—Diagram illustrating the union of a sodium atom and a chlorine atom to form a sodium chloride molecule. What happens to the sodium atom during the reaction?

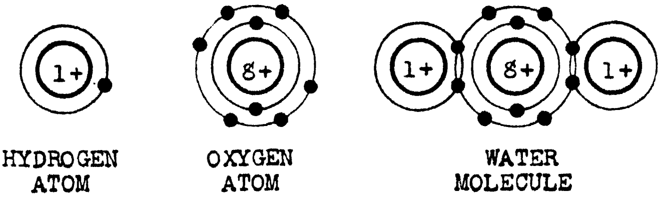


Fig. 6.—Diagrams illustrating the supposed structures of the hydrogen atom, the oxygen atom, and the water molecule. How does covalence differ from electrovalence?

Ionization.—When certain compounds, called *electrolytes,* are dissolved in water, the solutions formed will conduct an electric current. Other compounds, called *non-electrolytes,* do not have this ability. In 1887 Arrhenius, a Swedish chemist, formulated the *theory of ionization.* This theory assumes that when electrolytes are dissolved in water, some of their molecules split apart into separate particles. These particles are assumed to be the atoms or radicals of which the molecules are composed, except that, in separating from each other, *the atoms or radicals acquire an electric charge equal to their valence.* The electrolyte, Na_2SO_4, contains 2 sodium atoms (valence 1+) and 1 sulfate radical (valence 2–) in each molecule. When this substance is dissolved in water, some of its molecules are thought to dissociate (split apart), as indicated by the following *ionization equation:*

$$Na_2SO_4 \rightleftarrows 2\ Na^+ + SO_4^{--}$$

Each of the charged sodium particles (sodium *ions*) has a charge equal to its valence (1+). The sulfate particle, called a sulfate *ion,* has a charge of 2–, since its valence is 2–. The electric current is assumed to be conducted across the solution by these charged ions.

A double arrow was used in writing the above ionization equation. Whenever 2 sodium ions and a sulfate ion "bump" or come together in the solution, a sodium sulfate molecule (Na_2SO_4) is formed. After a short space of time this molecule again dissociates into ions. The double arrow, then, indicates that both molecules and ions are being formed constantly in the solution.

If we refer again to Fig. 5, we see that the sodium chloride molecule is really composed of a *sodium ion united to a chloride ion.* If sodium chloride is dissolved in water, the ions of which the molecule is composed separate, as indicated by the ionization equation:

$$NaCl \rightleftarrows Na^+ + Cl^-$$

Electrolytes, then, are substances whose molecules contain atoms or radicals united to each other by electrovalence. If the molecules of a substance contain only covalent linkages, the substance is a non-electrolyte.

Acids, Bases, and Salts.—Electrolytes are classified as acids, bases, or salts. Acids form hydrogen ions in solution; bases (alkalies) form hydroxide ions (OH^-) in solution; and salts in solution form neither hydrogen nor hydroxide ions. Examples of acids, bases, and salts are given in Table IV.

Salts and water are formed whenever acids react with bases. This type of reaction is called a *neutralization reaction.*

$$HCl + NaOH \rightarrow NaCl + H_2O$$
$$H_2SO_4 + Ba(OH)_2 \rightarrow BaSO_4 + 2\ H_2O$$

TABLE IV

SOME ACIDS, BASES, AND SALTS

Acids	
Hydrochloric acid (muriatic acid)	$HCl \rightleftarrows H^+ + Cl^-$
Sulfuric acid (oil of vitriol)	$H_2SO_4 \rightleftarrows 2\ H^+ + SO_4^{--}$
Nitric acid (aqua fortis)	$HNO_3 \rightleftarrows H^+ + NO_3^-$
Phosphoric acid (orthophosphoric acid)	$H_3PO_4 \rightleftarrows 3\ H^+ + PO_4^{---}$
Carbonic acid (CO_2 in water forms traces)	$H_2CO_3 \rightleftarrows H^+ + HCO_3^-$
Acetic acid (acid in vinegar)	$CH_3COOH \rightleftarrows CH_3COO^- + H^+$
Bases	
Sodium hydroxide (caustic soda)	$NaOH \rightleftarrows Na^+ + OH^-$
Potassium hydroxide (caustic potash)	$KOH \rightleftarrows K^+ + OH^-$
Calcium hydroxide (slaked lime; solution known as limewater)	$Ca(OH)_2 \rightleftarrows Ca^{++} + 2\ OH^-$
Ammonium hydroxide (solution known as ammonia water)	$NH_4OH \rightleftarrows NH_4^+ + OH^-$
Salts	
Sodium chloride (table salt)	$NaCl \rightleftarrows Na^+ + Cl^-$
Potassium sulfate	$K_2SO_4 \rightleftarrows 2\ K^+ + SO_4^{--}$
Calcium sulfate (gypsum; alabaster; known as plaster of Paris when dry)	$CaSO_4 \rightleftarrows Ca^{++} + SO_4^{--}$

Oxidation and Reduction.—Chemical reactions accompanied by a change in valence are called *oxidation-reduction reactions.* If no change in valence results, the reaction is a *metathetic reaction.* The substance that gains positive valence is *oxidized,* and the substance that loses positive valence (i.e., gains negative valence) is *reduced. Oxidation never occurs without a simultaneous reduction.*

When zinc reacts with hydrochloric acid, zinc chloride and hydrogen gas are produced.

$$\overset{0}{Zn} + 2\ \overset{1+}{H}\overset{1-}{Cl} \rightarrow \overset{2+}{Zn}\overset{1-}{Cl_2} + \overset{0}{H_2}$$

If we remember that *elements that are not combined with other elements have zero valence,* it is clear that the valence of zinc changes from 0 to 2+ when the above reaction takes place. Since this represents a gain in positive valence, *zinc is oxidized.* On the other hand, the valence of hydrogen changes from 1+ to 0. Therefore, *hydrogen is reduced,* because it loses positive valence. Chlorine is neither oxidized nor reduced; its valence does not change.

When hydrogen reacts with oxygen, the hydrogen is oxidized and the oxygen is reduced.

$$2\ \overset{0}{H}_2 + \overset{0}{O}_2 \rightarrow 2\ \overset{1+}{H}_2\overset{2-}{O}$$

Two useful rules to remember are these: (1) *Any substance that gains oxygen or loses hydrogen has been oxidized.* (2) *Any substance that gains hydrogen or loses oxygen has been reduced.*

Substances that are themselves reduced in chemical reactions are called *oxidizing agents,* because they bring about the oxidation of another substance. In the above example, oxygen was an oxidizing agent, because it caused the oxidation of the hydrogen. *Reducing agents* are oxidized in chemical reactions, and thus cause the reduction of some other substance. Hydrogen acted as a reducing agent in the foregoing example.

Study Questions

1. Give definitions for the following: chemistry, element, compound.
2. How many elements are known to exist in nature?
3. Give three illustrations of chemical change. How does a chemical change differ from a physical change?
4. What is a catalyst? What are enzymes?
5. Who first stated the atomic theory?
6. List six important properties of atoms.
7. At what temperature should all linear atomic motion cease? Have scientists succeeded in reaching this temperature?
8. Define: atom, molecule.
9. What is the atomic weight of oxygen? What element is used as a standard for the determination of atomic weights?
10. How do you define molecular weight?
11. Calculate the molecular weights of the following compounds: Na_2SO_4, CaS, $NaHCO_3$.
12. Define: gram-atomic weight, gram mole, mole.
13. State Avogadro's law. How many molecules are there in one mole of sodium chloride? In one mole of potassium nitrate?
14. Name nine subatomic particles. Which of these have not yet been proved to exist?
15. Carbon has an atomic numbr of 6 and an atomic weight of 12. Draw a diagram of the carbon atom.
16. How many protons are there in the nucleus of the carbon atom? How many neutrons?
17. How many electrons can be present in the first electron shell of an atom? In the second electron shell?

18. Make up a definition for an isotope. Give a reasonable explanation for the fact that the atomic weight of cadmium (112.41) is not a whole number.
19. List atomic symbols for the following elements: aluminum, copper, mercury, silver, zinc, bromine, sulfur, hydrogen, and iodine.
20. Write the shorthand expression for "6 gram moles of magnesium."
21. What figure is never written in chemical shorthand?
22. Balance the following equations:

$$BaCl_2 + K_2CO_3 \rightarrow KCl + BaCO_3$$
$$NaOH + H_2SO_4 \rightarrow Na_2SO_4 + H_2O$$

23. Complete and balance the following equation:

$$ZnCl_2 + H_2S \rightarrow$$

24. State the law of conservation of matter.
25. What is a radical? Give shorthand expressions for the following radicals: ammonium, sulfate, nitrate, phosphate, carbonate.
26. Make up a definition for valence.
27. As a rule, metals will not combine with hydrogen. Would you expect the valence of most metals to be positive or negative?
28. Write formulas for compounds composed of:
    (a) Calcium and bromine.
    (b) Aluminum and oxygen.
    (c) Potassium and the nitrate radical.
29. Explain the difference between electrovalence and covalence.
30. What is the most probable valence of an element whose atoms have only two electrons in their outer electron shells?
31. Define: electrolytes, non-electrolytes, ion, ionization.
32. Who first formulated the theory of ionization?
33. Write ionization equations for the following electrolytes: $Ca(NO_3)_2$, $NaHCO_3$, KBr.
34. Why is a double arrow used in writing ionization equations?
35. What type of valence linkage must be present in the molecules of an electrolyte?
36. Define: acid, base, salt. Give three examples of each.
37. Write three equations illustrating neutralization reactions.
38. Define: oxidation-reduction reaction, metathetic reaction.
39. What is oxidized when zinc combines with sulfur to form zinc sulfide? What is reduced?
40. Can oxidation ever occur without reduction?
41. When sugar combines with oxygen in the body, is the sugar oxidized or reduced?
42. Define: oxidizing agent, reducing agent. Give three examples of each.

CHAPTER II

PARTICLES IN SOLUTION

Solutions.—Intimate mixtures of molecules, atoms, or ions are called *solutions*. If a lump of sugar is placed in the bottom of a cup of coffee, the individual sugar molecules will diffuse in all possible directions (remember that molecules and atoms are in constant motion) until, very soon, the average number of sugar molecules in every teaspoonful of coffee will be the same. We say the sugar has *dissolved* in the coffee. Sugar, the substance that was dispersed in the coffee, is the *solute;* coffee, the liquid in which the solute was dispersed, is the *solvent*.

Chemical substances and mixtures can exist as liquids, gases, or solids. For this reason, a number of types of solution are possible. For example, the air we breathe is a solution composed of gases dissolved in other gases. The amalgams used in filling decayed teeth are solutions of metals in other metals (solids in solids). Most of the solutions in which we shall be interested, however, will be composed of solids dissolved in liquids, liquids dissolved in other liquids, or gases dissolved in liquids.

Temperature has a marked effect on the solubility of solutes—that is, on the amount of solute that can be made to go into solution in a given volume of solvent. As a general rule, solubility is increased by raising the temperature. Although only 13 g. of potassium nitrate will dissolve in 100 cc. of water at 0° C., 247 g. can be made to dissolve in the same volume at 100° C. Gases are exceptions to this general rule, because the solubility of a gas in a liquid is greatest when the temperature is low. Many gases are almost insoluble in water at 100° C. Calcium hydroxide is another exception. A total of 0.17 g. of this substance will dissolve in 100 cc. of water at 15° C.; only 0.077 g. can be dispersed in the same volume of water at 100° C. *Limewater* is a solution of calcium hydroxide.

Methods of Expressing Concentrations of Solutions.—*Percentage solutions.* The term "per cent" is a contraction of the

Latin phrase, *per centum,* which means "in one hundred." A 1 per cent (1%) solution contains one part of solute in 100 parts of solution. If 10 g. of sodium chloride (table salt) are dissolved in enough water so that the weight of the solution is 100 g., the resulting solution is described as a 10 per cent *by weight* solution of sodium chloride. If, on the other hand, 100 cc. of solution contain 10 g. of salt, the solution is a 10 per cent *by volume* solution. Notice that the phrases, *by weight* and *by volume,* tell us whether the one hundred parts of solution are measured in weight units (g.) or in volume units (cc.). If we fail to write down one of these phrases, we imply that the solution was prepared by dissolving the solute in enough solvent to make 100 g. of solution.

Molar solutions. When one mole of a substance is dissolved in enough solvent to make a volume of one liter, the solution formed is called a *molar* (1 *M*) *solution.* The molecular weight of KCl is 74.55. A 0.1 M solution of this compound is prepared by weighing out 7.455 g. of KCl, placing it in a suitable container, and dissolving it in sufficient water to make a final volume of one liter. This method of expressing concentration is useful to the chemist, since it enables him to obtain the number of moles (or fractions of a mole) he requires simply by measuring a volume, a procedure much quicker than weighing the substance on a delicate chemical balance.

Normal solutions. The *equivalent weight,* or *gram-equivalent weight,* of a substance (element or compound) is that weight which will furnish, react with, or displace one gram-atomic weight (1.0081 g.) of hydrogen. Methods for calculating equivalent weights will be described briefly.

1. *Equivalent weights of elements.* The valence of combined hydrogen is unity (1+). Therefore, one gram-atomic weight of hydrogen will combine with, or will be displaced by, exactly one gram-atomic weight of other elements whose valence is 1. Elements whose valence is 2 can combine with, or displace, exactly two gram-atomic weights of hydrogen, and so on. Therefore, the equivalent weight of an element can be calculated by *dividing its gram-atomic weight by its valence.* For example, the

atomic weight of iodine is 126.92. Since the valence of combined iodine is 1–, the gram-equivalent weight of iodine is 126.92 g. Calcium has an atomic weight of 40.08 and a valence of 2+; thus its equivalent weight is 20.04 g. The equivalent weight of aluminum, which has an atomic weight of 26.97 and a valence of 3+, is 8.99 g.

2. *Equivalent weights of acids.* All acids contain replaceable hydrogen, that is, hydrogen that can be replaced by some other element in the course of a chemical reaction. The equivalent weight of an acid is calculated by *dividing the gram-molecular weight of the acid by the number of replaceable gram-atomic weights of hydrogen.* Hydrochloric acid (HCl) has one replaceable hydrogen atom; thus the equivalent weight of HCl is the same as its molecular weight (36.47 g.). Sulfuric acid (H_2SO_4), which has two replaceable hydrogen atoms in each molecule and a molecular weight of 98.08, has an equivalent weight of 49.04 g.

3. *Equivalent weights of bases.* Bases contain OH radicals in their molecules. Since the valence of this radical is 1–, the equivalent weight of a base is calculated by *dividing its gram-molecular weight by the number of OH groups in each molecule.* Sodium hydroxide (NaOH) has a molecular weight of 40.01; its equivalent weight, therefore, is 40.01 g. Barium hydroxide, $Ba(OH)_2$, has a molecular weight of 271.38 and an equivalent weight of 135.69 g.

4. *Equivalent weights of salts.* Most salts contain neither replaceable hydrogen atoms nor hydroxyl radicals in their molecules. All of them, however, contain a radical or atom of positive valence combined with a radical or atom of negative valence. The equivalent weight of a salt can be computed by *dividing the gram-molecular weight by the valence of the positive radical (radicals) or atom (atoms).* The ammonium radical (NH_4) has
lence of 1+; hence the equivalent weight of ammonium chlo-
NH_4Cl) is 53.50 g., since the molecular weight of this salt
Calcium sulfate ($CaSO_4$), the calcium of which has a
f 2+, has a molecular weight of 136.14 and an equivalent

weight of 68.07 g. Each sodium atom in a molecule of sodium carbonate (Na_2CO_3) has a valence of 1+. However, the *total* positive valence of the molecule is 2+, and the equivalent weight (53.00 g.) of sodium carbonate is found by dividing its molecular weight (105.99) by 2.

5. *Equivalent weights of oxidizing agents.* When an oxidation occurs, at least one of the atoms present in the molecule of oxidizing agent gains electrons (that is, loses positive valence). In the reaction,

$$2\,K\overset{7+}{Mn}O_4 + 5\,CaC_2O_4 + 8\,H_2SO_4 \rightarrow K_2SO_4 + 2\,\overset{2+}{Mn}SO_4 + 5\,CaSO_4 + 10\,CO_2 + 8\,H_2O,$$

each of the manganese atoms present in a molecule of the oxidizing agent (potassium permanganate) gains 5 electrons—that is, loses 5 positive valences. Since hydrogen is able to gain or lose only 1 electron when it takes part in an oxidation-reduction reaction, the equivalent weight of potassium permanganate (31.61 g.) is determined by dividing its molecular weight (158.03) by 5.

A solution that contains one gram-equivalent weight of substance in one liter of solution is called a ***normal (1 N) solution.*** A 0.1 N solution of sulfuric acid thus contains 4.904 g. of H_2SO_4 per liter. A 0.05 N solution of potassium permanganate contains 1.581 g. of $KMnO_4$ per liter, and so on.

Normal solutions are particularly useful to the chemist, because ***equal volumes of solutions of equal normality will react exactly with each other*** (provided, of course, the substances in the solutions are capable of undergoing reaction). For example, 10 cc. of 0.05 N sodium hydroxide will neutralize ***exactly*** 10 cc. of 0.05 N sulfuric acid. When the normalities of the reacting solutions are not identical, the amounts of solution required readily can be calculated if the normalities are known. Suppose we wish to neutralize 100 cc. of 0.1 N barium hydroxide solution with 0.2 N hydrochloric acid. Since the normality of the drochloric acid is twice that of the barium hydroxide, onl as much of the acid solution (50 cc.) will be required fo neutralization.

The pH Notation.—When water ionizes, equal numbers of hydrogen ions and hydroxide ions are formed.

$$H_2O \rightleftarrows H^+ + OH^-$$

Only about one molecule out of every 555,000,000 molecules of water is ionized at ordinary temperatures. Nevertheless, it is important to remember that both hydrogen and hydroxide ions will be present in every water solution. If the concentration of hydrogen ions, $[H^+]$, is greater than the concentration of hydroxide ions, $[OH^-]$, the solution is acid; if $[OH^-]$ is greater than $[H^+]$, the solution is basic; and, if $[H^+]$ equals $[OH^-]$, the solution is neutral.

$[H^+]$ and $[OH^-]$ are related to each other by the fundamental equation:

$$[H^+] \times [OH^-] = 10^{-14} = \frac{1}{10^{+14}} = \frac{1}{100{,}000{,}000{,}000{,}000} = 0.00000000000001.$$

The concentration of hydrogen ions is said to be 1 when the solution contains an equivalent weight (1.0081 g.) of hydrogen ions per liter. The concentration of hydroxide ions is 1 when the solution contains 17.0081 g. of hydroxide ions per liter, since the equivalent weight of the OH radical is 17.0081. The figure, 10^{-14}, in the above expression thus refers to gram-equivalent weights.

In the special case where $[H^+] = [OH^-]$, we may write:

$$[H^+]^2 = 10^{-14}, \text{ or } [H^+] = 10^{-7}.$$

In other words, a neutral solution (i.e., a solution in which $[H^+] = [OH^-]$), contains 10^{-7} gram-equivalent weights of hydrogen ions per liter.

The term pH, an abbreviation for "power function of $[H^+]$," is defined by the equation,

$$[H^+] = 10^{-pH}.$$

Since the hydrogen-ion concentration of a neutral solution is 10^{-7}, *the pH of a neutral solution is 7.** In acid solutions $[H^+]$

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*pH may be defined also by the expression, $pH = \log_{10} \frac{1}{[H+]}$. Since the hydrogen-ion concentration of a neutral solution is 10^{-7}, $pH = \log_{10} \frac{1}{10^{-7}} = \log_{10} 10^7 = \log_{10} 10{,}000{,}000 = 7$.

is always greater than 10^{-7}, and the pH is always *less than 7.* For example, the concentration of hydrogen ions in a 0.01 N solution of HCl is approximately 0.01 (10^{-2}), and the pH is approximately 2. In basic (alkaline) solutions $[H^+]$ always is less than 10^{-7}, and the pH is *greater than 7.* A 0.01 N solution of NaOH contains approximately 10^{-2} gram equivalents of hydroxide ion per liter. Since $[H^+] \times [OH^-] = 10^{-14}$, the hydrogen-ion concentration of the solution will be 10^{-12}, and the pH will be 12.

Notice that a change of one pH unit indicates a tenfold change in hydrogen-ion concentration. This relationship is illustrated by the following comparisons:

	$[H^+]$	pH	$[OH^-]$
Acid solutions			
	1 (10^0)	0	10^{-14}
	10^{-1}	1	10^{-13}
	10^{-2}	2	10^{-12}
	10^{-3}	3	10^{-11}
	10^{-4}	4	10^{-10}
	10^{-5}	5	10^{-9}
	10^{-6}	6	10^{-8}
Neutral solution			
	10^{-7}	7	10^{-7}
Basic solutions			
	10^{-8}	8	10^{-6}
	10^{-9}	9	10^{-5}
	10^{-10}	10	10^{-4}
	10^{-11}	11	10^{-3}
	10^{-12}	12	10^{-2}
	10^{-13}	13	10^{-1}
	10^{-14}	14	1 (10^0)

Osmotic Pressure.—Let us imagine that a container is divided into two equal halves by means of a membrane (see Fig. 7). This membrane, we shall assume, contains numerous small pores. In compartment A we place a cane sugar solution; in compartment B, distilled water only. Since all molecules are in constant motion (except at –273° C.), the sugar and water molecules gradually pass through the pores in the membrane until the concentration of sugar is the same in both compartments.

Suppose the experiment is repeated, except that this time the membrane we use is *semipermeable,* that is, it has pores large enough for water molecules to pass through, but too small to permit the passage of sugar molecules. Both sugar and water molecules will strike the A side of the membrane, but only the water molecules can pass into compartment B. On the other hand, every molecule that strikes the B side of the membrane will be a water molecule, and can pass into compartment A. Water thus will flow across the membrane in both directions, but *more water will pass into compartment A than into compartment B,* simply because more water molecules strike the membrane on the B side. As time goes on, the amount of fluid in compartment A gradually will increase, and that in compartment B will decrease. Finally, the weight of the extra fluid in compartment A becomes great enough to force water molecules back into compartment B as rapidly as they pass in the reverse direction, and thereafter the volumes of fluid in the two compartments will not change. The pressure (force per unit area) exerted by the weight of the *extra* water in compartment A when this stationary (equilibrium) state is reached is a measure of the *osmotic pressure* of the final sugar solution.

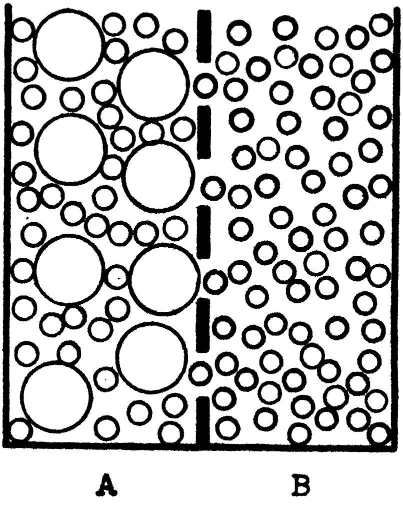

Fig. 7.—Diagram illustrating osmotic pressure. The large circles represent sugar molecules; small circles represent water molecules. In a given time, will more water molecules move from compartment A to compartment B, or in the opposite direction?

It has been found that all 1 M solutions of non-electrolytes have exactly the same osmotic pressure. Since all such solutions contain the same number (6.06×10^{23}) of molecules per liter, we reach the conclusion that the magnitude of the osmotic pressure is determined by the *number* of dissolved particles in a given volume. The *size* of the dissolved particles is unimportant.

Let us suppose that a 1 M sugar solution is placed in compartment A of the apparatus illustrated in Fig. 7. We have learned already that the volume of fluid in compartment A gradually will increase. However, imagine that we exert pressure on the surface of the sugar solution just sufficient to prevent any change in volume. This pressure will be equal in magnitude to the osmotic pressure. When this type of experiment is carried out, it is found that the osmotic pressure of a 1 M solution of non-electrolyte is 22.4 atmospheres—that is, 22.4 times as great as the pressure exerted by the atmosphere at sea level. A column of mercury 760 mm. high exerts the same pressure as one atmosphere at sea level. If, then, we are told that a given solution of non-electrolyte has an osmotic pressure of 760 mm. of mercury, it is not difficult for us to calculate that the concentration of the solution is $\frac{1}{22.4}$ molar.

When a strong electrolyte, such as KCl, is dissolved in water, it dissociates into ions. If we remember that the osmotic pressure is determined by the concentration of dissolved particles, and not by the concentration of molecules, it becomes apparent that a 1 M solution of KCl will have nearly twice the osmotic pressure of a 1 M solution of non-electrolyte. Each of the solutions contains the same number of dissolved *molecules* per liter, but most of the electrolyte molecules ionize to form K^+ and Cl^-. In other words, the number of *particles* in a given volume of the electrolyte solution is approximately twice as great as the number present in the same volume of the non-electrolyte solution.

Most of the molecules of a *weak* electrolyte, such as acetic acid, are present in solution in undissociated form. Therefore, the osmotic pressure of an acetic acid solution is somewhat greater than that of a cane sugar solution, and less than that of a potassium chloride solution, of the same molar concentration.

Solutions that have the same osmotic pressure are said to be *isotonic;* or, we may say they have the same *osmolar concentrations. Hypertonic* and *hypotonic* solutions have, respectively, greater and lesser osmolar concentrations than some reference solution. Biochemists interested in animal metabolism often use plasma (the liquid portion of the blood) as a reference solution. The osmotic pressure of human blood plasma is approximately 5,200 mm. of mercury (6.9 atmospheres).

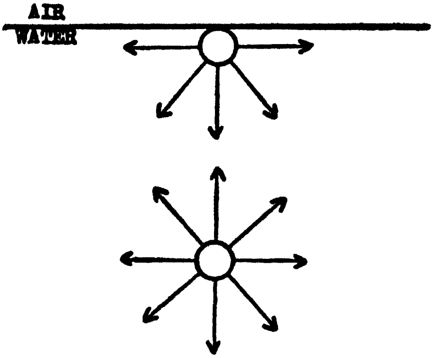

Fig. 8.—Diagram illustrating surface tension. The arrows indicate the directions in which the water molecules (circles) are attracted by other molecules. Explain how surface active substances lower the surface tension of water.

Boiling and Freezing Points of Solutions.—Water boils at 100° C. and freezes at 0° C. However, a molar solution of a non-electrolyte in water boils at 100.51° C. and freezes at –1.86° C. This elevation of the boiling point and lowering of the freezing point of water when a solute is present depend, as does osmotic pressure, on *the number of particles* (*atoms, molecules, ions*) *present in a given volume of the solution.* The change in boiling and freezing points caused by the presence of a mole of KCl in a liter of solution is nearly twice as great as that resulting from the presence of a mole of non-electrolyte in the same volume of solution.

Surface Tension.—Molecules and atoms attract each other in much the same way that the sun attracts the earth. A molecule in the middle of a beaker of water is attracted in all possible directions by the other water molecules that surround it (see Fig. 8). The situation is different for a molecule located in the surface of the water. Such a molecule is attracted downward and sideways by other molecules, but it cannot be attracted upward very much. This unequal distribution of forces causes the molecules in the surface to pack tightly together. The force required to break through this film of closely packed surface molecules is equal to the *surface tension* of the water. All liquids exhibit surface tension, but the surface tension of water is higher than that of most other liquids.

Suppose some olive oil is allowed to float on the surface of water. Water molecules in the surface now will be attracted in all directions—sideways and downward by other water molecules, and upward by molecules in the olive oil. However, the attractive force between individual water molecules is greater than that between water molecules and the molecules in the olive oil. Consequently, the forces attracting the surface water molecules downward and sideways will be greater than those attracting them upward. The effect of the olive oil, then, is not to abolish the surface tension of the water, but only to lower it. Substances, such as the compounds in the olive oil, that tend to collect at water surfaces are called *surface active substances,* because they lower the surface tension of the water.

As we have seen, the tension between a liquid and air is called the surface tension of the liquid. Often the term *interfacial tension* is used to designate the tension between two liquids, or between a liquid and a solid.

Emulsions.—An *emulsion* is formed whenever tiny droplets of one liquid are suspended in another liquid. If a small amount of mineral oil is shaken vigorously with a large volume of water, the mineral oil breaks up into many droplets which tend to become more or less uniformly distributed throughout the water (see Fig. 9). Such an emulsion is not stable, however, because the mineral oil drops coalesce to form larger and larger drops, and soon all the oil floats on top of the water.

Imagine a rubber sheet stretched tightly parallel to the floor. Now imagine that two small steel balls are placed on the sheet. The presence of these balls causes tension to develop in the rubber in their vicinity. As a result, they move toward each other until they touch. These balls may be compared with the droplets of mineral oil in an emulsion. The tension between the oil drops and the water (interfacial tension) is similar to the tension of the rubber sheet. Consequently, the drops tend to approach each other, and the emulsion "breaks."

We have learned that water has a higher surface tension than most other liquids. Surface active substances lower this high surface tension with the result that the difference in tension between the water and the emulsified material becomes small. Since this difference in tension is the force that causes the coalescence of the suspended drops, the presence of a surface active substance makes an emulsion more permanent. Soaps, bile acids and salts, gums, and other surface active substances used to stabilize emulsions often are called *emulsifying agents.*

Colloidal Dispersions.—When particles whose diameters vary from 1 millimicron (10^{-7} cm.) to 100 millimicrons (10^{-5} cm.) are suspended in a liquid, the resulting mixture is called a *colloidal dispersion,* or *sol.* Unlike particles in true solution, that is, particles whose diameters are less than 1 millimicron, the particles of a colloidal dispersion are too large to pass through membranes made of parchment paper or animal tissues. *Suspensions* are formed when particles larger than 100 millimicrons are mixed with a liquid. Suspensions are not permanent, since the particles present in them are too large to remain suspended and soon settle to the bottom of the container.

Hydrophilic ("water-loving") sols are colloidal dispersions in which the suspended particles have an affinity for water. Each of the particles in such a sol is closely surrounded by a shell of *bound water.* The particles of a hydrophobic ("water-hating") sol do not have this water shell. In general, hydrophilic sols are more viscous and more permanent than hydrophobic sols, since their particles are protected by the bound water. Protein

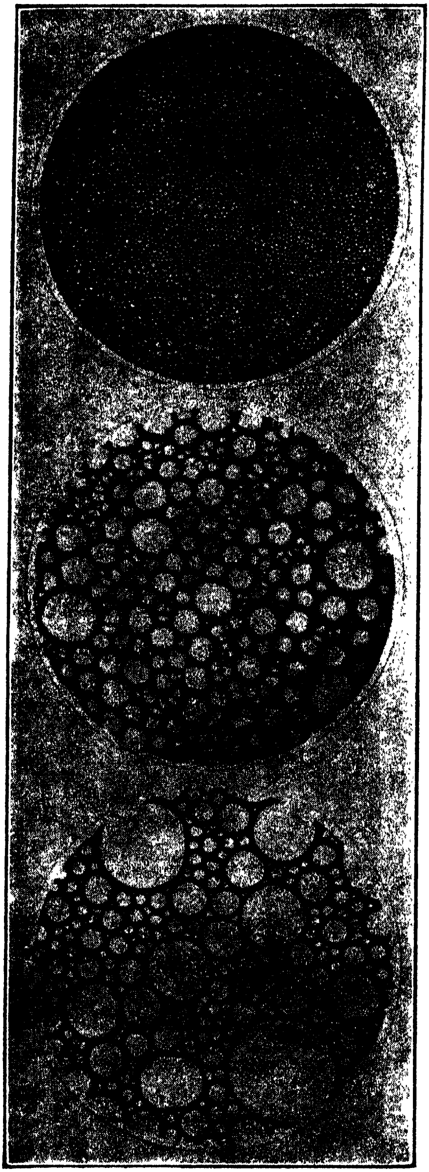

Fig. 9.—Photomicrographs (photographs taken through a microscope) of emulsions. What material emulsifies fat in the digestive tract? (From Patchwork, a publication of the E. L. Patch Co.)

solutions are examples of hydrophilic sols. If highly insoluble substances, such as gold, are dispersed in water, hydrophobic sols are formed.

When a beam of light is allowed to pass through an otherwise dark room, the path of the beam appears to be filled with fairly large particles of dust. This effect, called the *Tyndall effect,* is explained by the fact that some of the light rays strike microscopic particles in the air and are reflected at right angles. If we view the beam of light at right angles to its course, the reflected light rays that reach our eyes will be perceived as bright spots in the beam. Colloidal dispersions also show the Tyndall phenomenon; that is, they appear cloudy when they are viewed at right angles to a beam of light passing through them. True solutions do not exhibit this effect, because the particles present in them are too small to reflect the light.

Colloidal particles have a positive or negative electrical charge. This charge may result from the ionization of molecules in the surface of the particle, or it may be due to the fact that ions in the surrounding solution have stuck to (been adsorbed by) the surface of the colloidal particle. Sols are stabilized by the presence of these electrical charges. For example, the particles in a gold sol are negatively charged. Since like charges repel each other, the particles of gold are prevented from coalescing to form particles too large to remain suspended. Hydrophobic sols, such as a gold sol, can be coagulated by the presence of an electrolyte, such as sodium chloride. The positive sodium ions, formed when the sodium chloride is dissolved, neutralize the negative charges of the gold particles, and the gold precipitates. Hydrophilic sols, which are protected not only by the electrical charge, but also by bound water, are not so readily coagulated by electrolytes.

If a sol is placed in an electric field, that is, between the positive and negative poles of an electric circuit, the colloidal particles will migrate toward one of the electric poles. Since opposite charges attract each other, negatively charged particles will move in the direction of the positively charged pole (anode), and positively charged particles will move toward the negatively charged pole (cathode). The movement of colloidal particles under the influence of an electric field is called *electrophoresis* or *cataphoresis.*

If two hydrophobic sols of opposite electric charge are mixed, the negatively charged particles of the one unite with the positively charged particles of the other and *mutual coagulation* occurs. This type of coagulation is irreversible; that is, the coagulated particles cannot be made to go into colloidal dispersion again.

The mixing of two hydrophilic sols of opposite charge also results in coagulation. The coagulated particles are not in actual contact with each other, however, because each of them is surrounded by a water shell. This type of coagulum is called a *coacervate.* The particles of a coacervate may be redispersed by the addition of an electrolyte. The ions formed from the electrolyte neutralize the electric charges holding the hydrated particles together.

The area of particles in colloidal dispersion is relatively enormous. The area of a cube of gold whose edges are 1 cm. long is 6 cm.^{2} (6 sq. cm.). If this cube is divided into cubes of colloidal size, for example, into cubes whose edges are 10 millimicrons (10^{-6} cm.), the area of all the small cubes will be 6,000,000 cm.^{2} Molecules or ions in true solution tend to stick to (be *adsorbed* by) colloidal surfaces. Surface active substances often are very readily adsorbed, because they tend to concentrate at the interface between the water and the colloidal particles. Undoubtedly, many essential substances are held in the cells of our bodies by adsorption. Powdered charcoal, which has a large surface, is used in gas masks to adsorb poison gases. Many colored surface active materials are used to dye cloth.

Membranes that permit the passage of molecules or ions in true solution, but which do not permit the passage of colloidal particles, are called *dialyzing membranes.* Probably most of the membranes in plant and animal tissues are of this type. The separation of colloidal particles from particles in true solution by means of a dialyzing membrane is called *dialysis.* Suppose we have a solution containing protein molecules and sodium chloride molecules. If this solution is placed in a bag made of a dialyzing membrane, and the bag is placed in running water, the sodium chloride molecules will gradually pass through the membrane into the running water. On the other hand, the protein molecules, which are of colloidal size, will remain in the bag. If this process is continued long enough, the protein solution will become free of salt. Dialysis frequently is used to remove contaminating substances from hydrophilic sols.

Study Questions

1. Define: solution, solvent, solute.
2. What are the three physical states in which substances exist?
3. List six possible types of solution.
4. What is the usual effect of temperature on the solubility of a solid? Of a gas?
5. If a warm bottle of soda water is opened, foam spouts from the bottle. Usually this does not occur if the soda water is cold. Explain.
6. What is limewater?
7. How much $CaCl_2$ will be required to make 100 cc. of a 5 per cent by volume solution of this substance?
8. How much sugar, and how much water, will be required to make 100 g. of a 15 per cent by weight solution of sugar?
9. How many grams of each of the following substances will be required to make 500 cc. of a 0.01 M solution? $NaHCO_3$, H_2SO_4, $Ca(NO_3)_2$, KOH.
10. Calculate the equivalent weight of each of the following: Ag, HNO_3, $Ca(OH)_2$, $CuCl_2$.
11. How many grams of each of the following substances will be required to make 500 cc. of a 0.01 N solution? H_3PO_4, $Cu(OH)_2$, $Fe(NO_3)_3$, Na_2SO_4.
12. Calculate the equivalent weight of the reducing agent in the following reaction: $Zn + H_2SO_4 \rightarrow ZnSO_4 + H_2$.
13. How many cubic centimeters of 0.1 N NaOH solution will be required to neutralize exactly 300 cc. of 0.025 N HCl solution?
14. Define pH.
15. Assuming complete ionization, what is the approximate pH of each of the following solutions? 0.1 N HCl, 0.1 N KOH, 0.1 N NaCl.
16. What is the pH of a neutral solution?
17. What change in hydrogen-ion concentration takes place when the pH is lowered from 8 to 4?
18. Make up a definition for osmotic pressure.
19. Ten grams of the non-electrolyte, $C_6H_{12}O_6$, are dissolved in enough water to make a volume of 1,000 cc. Calculate the osmotic pressure of the solution in atmospheres and in millimeters of mercury.

20. Calculate the approximate osmotic pressure of a 0.1 N solution of Na_2SO_4.
21. Calculate the approximate osmotic pressure of a 0.1 M solution of Na_2SO_4.
22. Define: isotonic solution, hypotonic solution, hypertonic solution.
23. Calculate the approximate boiling and freezing points of the following solutions: 0.15 M sugar solution, 0.15 M KCl solution.
24. A solution is found to freeze at -0.93° C. Calculate the osmotic pressure of the solution.
25. A solution has an osmotic pressure of 10 atmospheres. Calculate its approximate boiling point.
26. Make up a good definition for surface tension. For interfacial tension.
27. A steel needle will float if it is placed on the surface of water with sufficient care. If bile salt is then added to the water, the needle will sink. Explain.
28. What is a surface active substance?
29. Is the surface tension of water higher or lower than that of most other liquids?
30. What is an emulsion? An emulsifying agent? Give three examples of each that might be found in an average kitchen.
31. One type of mayonnaise can be made from olive oil, egg yolk, and vinegar. What is the function of the egg yolk?
32. How large are particles in colloidal dispersion?
33. How does a sol differ from a true solution? From a suspension?
34. How do hydrophilic sols differ from hydrophobic sols? Which type of sol is most stable?
35. Describe the Tyndall phenomenon. How is it explained?
36. What are the usual sources of the electrical charges present on colloidal particles?
37. Explain how the presence of electrical charges on colloidal particles helps to stabilize the sol.
38. What is the anode? The cathode?
39. What is meant by electrophoresis?
40. Explain why sols of opposite electrical charge undergo mutual coagulation when they are mixed.
41. What is a coacervate? How can the particles of a coacervate be made to redisperse?
42. Make up a definition for adsorption. How does it differ from absorption? (Use any good dictionary.)
43. Why do colloidal dispersions make good adsorbing agents?
44. Define: dialyzing membrane, dialysis.
45. Describe how you would separate sodium chloride molecules from a starch sol.

PART II

ORGANIC CHEMISTRY

CHAPTER III

SATURATED ALIPHATIC HYDROCARBONS

Introduction.—The practice of classifying chemical substances as either organic or inorganic had its beginning early in the history of chemistry. Compounds obtained from plant and animal substances were classed as organic compounds because it was thought that a mysterious agency known as "vital force" associated with living processes was necessary for their formation. The vital force theory was disproved by Wöhler in 1828, when he synthesized urea in the laboratory by heating ammonium cyanate, NH_4OCN. The synthesis from an inorganic substance of urea, which had long been known as the principal nitrogenous compound in human urine, encouraged the laboratory synthesis of many other compounds previously known only as the products of living processes. Hence, the original distinction between organic and inorganic compounds was no longer valid. The early chemists, however, observed that carbon was the essen [illegible] compounds formed by living processes [illegible] therefore, was the compounds of carbon exhibit a complexity of structure without parallel among the inorganic compounds. For example, the organic compound having the molecular formula of $C_{10}H_{22}$ can exist in 75 different forms that have different physical and chemical properties. Another reason for separating organic compounds into a distinct class is the existence of such a large number of compounds of carbon. Over 400,000 compounds of carbon are known, while there are only about 27,000 compounds of the other elements. In addition, organic compounds as a class are less stable than inorganic compounds. On heating, organic compounds turn dark and decompose.

Scope of Organic Chemistry.—Many students approach the study of organic chemistry with the feeling that it is going to be a difficult subject, that it is a necessary evil as a "prerequisite" to be disposed of as quickly as possible, and that it is related only vaguely, if at all, to their major field of interest. It is hoped that the following brief survey will help the prospective student to gain an idea of how the subject matter to be treated in Part II is definitely applicable to other subjects in his or her curriculum.

Some students, for example, will be interested in the discussion of the structure and properties of synthetic textile fibers, such as nylon, Vinyon, Aralac, and rayon, as well as the structure of the dyes that impart the manifold hues and shades to textiles made from these fibers. Studen[illegible] with the study of foods will fin[illegible] ins, fats sibilities for the utilization of such farm by-products as straw, oat hulls, corn cobs, and skim milk for the preparation of industrially important products. Large quantities of skim milk are used in the manufacture of several types of synthetic fibers.

Portions of the material will be of general interest. Such knowledge will make for a better appreciation and understanding of the role of organic chemistry in the processes affecting everyday life. For example, organic chemistry is intimately associated with the development of the rapidly growing plastics industry. The number of articles made of plastic materials for household, personal, and industrial uses is rising steadily. The pressure of war time called forth increased production of these synthetic substances, since they were used to replace metals. The airplane industry consumed large quantities of these materials. In general, they are light in weight and are durable. The transparent and moldable characteristics of methacrylate resins made them well suited for use in the making of cockpit enclosures and nose sections for bombing planes, as illustrated

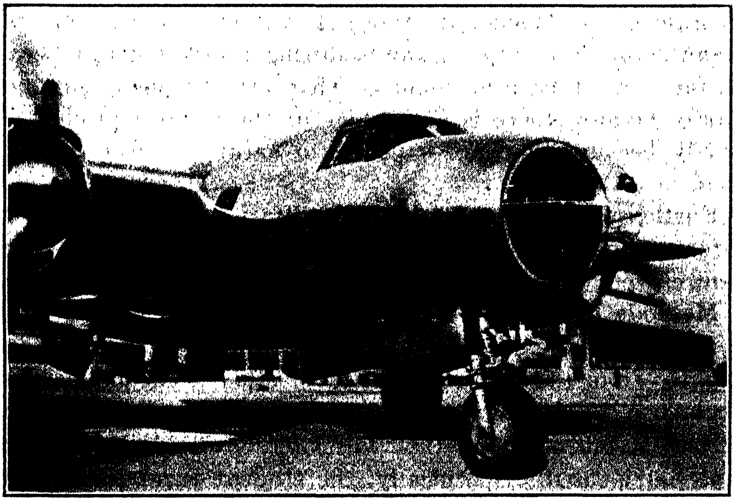

Fig. 10.—Martin B-26 medium bomber showing Plexiglas (methyl methacrylate) nose section in which the bombardier sits. (Courtesy of the Röhm and Haas Co., Inc., Philadelphia, Pa.)

in Fig. 10. The various types of plastic are discussed in connection with the organic compounds from which they are manufactured.

The valuable natural resource, petroleum, is treated in considerable detail. By-products from the cracking process, by which additional gasoline is obtained from petroleum, are being used for the manufacture of a wide range of other types of compound, such as glycerol, ethyl alcohol, toluene for the manufacture of T.N.T., and the material from which a number of the synthetic rubbers are made. Buna S (GR-S), Buna N, Butyl, Neoprene, and Thiokol are types of synthetic rubbers that were manufactured in large amounts during the recent war because of the lack of natural rubber. They are still being produced, partly because there is a shortage of the natural product and partly because they are superior to natural rubber for many uses.

Furthermore, apart from any utilitarian value, the type of information found in these pages will make for a more intelligent citizenry, so important in the perpetuation of a democracy.

Methods of Study.—In studying organic chemistry, the experience of many students has shown that a procedure differing slightly from that ordinarily used in other academic courses is necessary. This recommended procedure is to use that form of activity in studying that will later be demanded when the material is used. Specifically, the student is advised to write down on paper the equations and formulas. *Organic chemistry cannot be mastered without the use of pencil and paper.* A careful reading of the descriptive material and equations may give the student the impression that he has learned the subject matter and can use it, but when he comes to writing equations or formulas, he will find that he often is not quite sure of the position of a particular group, or perhaps the number of carbon atoms in a compound. *The fact that the only efficient and effective method of learning the material of organic chemistry is by the actual writing of the formulas and equations cannot be emphasized too strongly.*

An individual may say, and truthfully so, that he has forgotten more than another ever knew, but this surely is no credit

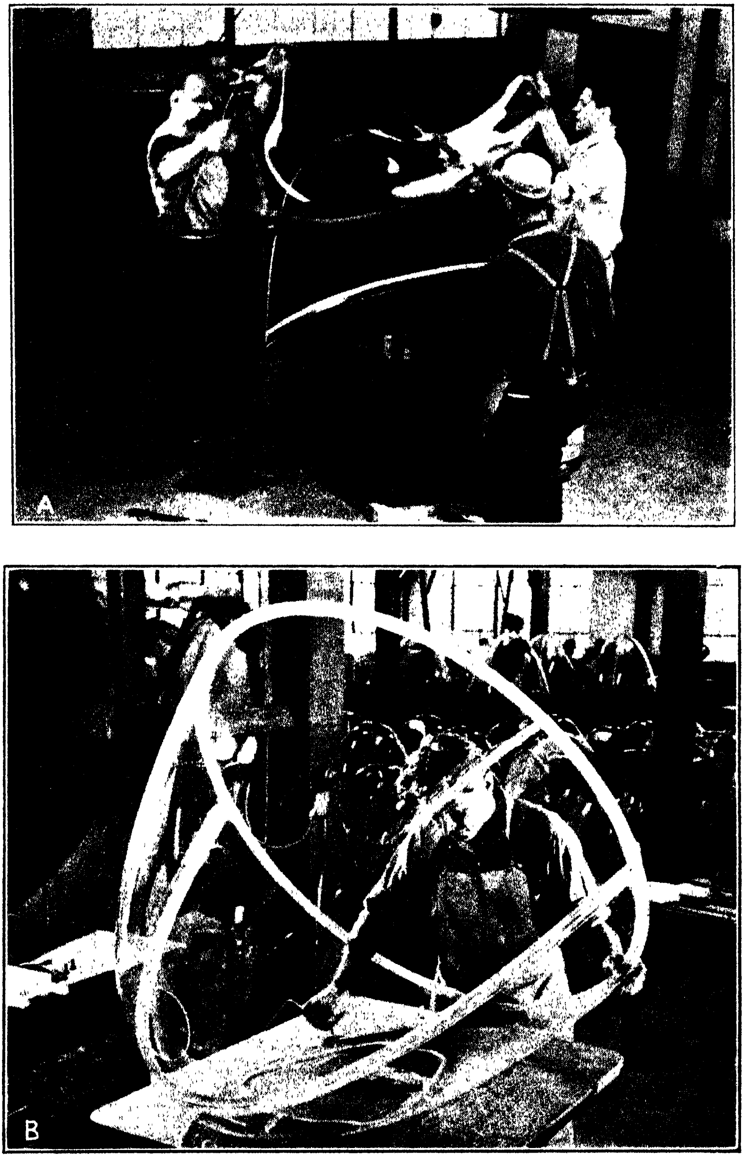

Fig. 11.—*A*, Manufacture of Plexiglas (methyl methacrylate) nose sections for the Martin B-26 bomber. Skilled workmen are draping a hot sheet of the plastic over a cloth-covered form. The edges are clamped quickly before the material cools. After cooling the material retains its shape. *B*, Workman trimming the edges of a bombardier's door and the gun-mount hole. The formed halves of the bomber nose are cemented with methyl methacrylate resin, the same resin as used originally to make the Plexiglas sheets. (Courtesy of the Röhm and Haas Co., Inc.)

to himself. Material to be worth while must be capable of being recalled. The three most important factors in the recall of facts or information are: (1) vividness of the first impression; (2) association; and (3) repetition.

In the study of organic chemistry it is somewhat difficult to utilize fully the powerful first factor in recall. The lecture demonstrations by the instructor and exhibits are helpful, but not all material lends itself to this possibility. If the student could witness a fire and an explosion as examples of reactions of certain organic compounds, it would be much easier to remember them, but fortunately or unfortunately, depending on one's point of view, this is not possible.

The factor of association in recall is more easily utilized or applied. The association of formula and the name of organic compounds is very important. The sight of either one should be a visual stimulus for the recall of the other. As an aid in strengthening this association, equations throughout the text give the name of the organic compound directly beneath its formula. The student should use his own experiences gained through inspection tours, vacation trips, travels during the recent war, etc., to aid him in recalling formulas and properties of compounds. For example, suppose an individual has visited an oil refinery. At the time he may not have appreciated fully the guide's description of the processes or substances involved, but when the subject of petroleum is discussed in the text, it will have added meaning because of the associaton of the subject matter with an actual experience.

The third factor in recall, repetition, is perhaps the least pleasant but oftentimes the most effective. Studying should not become drudgery, but the homely observation that the continual dropping of water, even on granite, will finally make an impression is not without its application to this problem. Students should not hesitate to drill themselves, especially when learning fundamental principles.

Another admonition, which is the result of observation of several thousand students over a period of years, is that the student should begin to study immediately at the start of the course. If studying is postponed, material accumulates and the delay in learning necessary principles interferes with the learning of later material, and the student is apt to find himself confronted with a discouragingly large amount of material to assimilate.

The mastery of the general principles is admittedly the primary aim, but because of the nature of organic chemistry, a considerable body of facts and details also must be learned in order to apply the general principles intelligently. Possibly due to the body of facts that must be learned, there is a tendency on the part of students to memorize facts without thinking about their significance or their relationship to other facts. This practice is deplorable, especially as manifested in the "cramming" for examinations. Material that is learned with the thought in mind that it is merely for the examination on the following morning, is likely to be retained only that long. The student should realize that he is acquiring this information for his own use as a preparation for the future, and not merely to satisfy a prerequisite or an advisor.

As a final word of advice, the student is urged to cultivate efficient habits of study. He should have a quiet place in which to work and a definite study period; he should brook no interruptions. At the end of the study period he should test himself on the results of his study. The questions at the end of the chapters may be of assistance, and in addition the student should formulate questions and outlines of his own.

Structure of the Carbon Atom.—Organic chemistry has been defined as the chemistry of carbon compounds; hence it is proper and fitting that we consider the structure of the carbon atom. Since the carbon atom has four electrons in its outer shell, the valence (or combining power) should be 4.* This has been shown to be true. The first fundamental concept of organic

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*The atomic number of carbon is 6, and since there are always two electrons in the first shell (orbit), there will be four electrons in the second shell (see page 25). The most stable configuration for atoms is the presence of eight electrons in the outer shell; therefore, in chemical reactions there is a tendency for atoms to acquire this stable arrangement. In most organic compounds the stable arrangement is gained by a sharing of electrons with some other atom. This type of linkage in which the valence electrons are shared is termed *covalence*. It is described also as a non-ionizing bond. Many organic compounds do not ionize; hence they do not conduct an electric current (page 35).

chemistry, accordingly, is that the *valence of carbon is 4.* The student will make his study of organic chemistry much easier if he constantly keeps this fact in mind.

The simplest organic compounds are those that contain only carbon and hydrogen. This class of compounds is known as *hydrocarbons.* A molecule of the simplest hydrocarbon must contain one carbon atom and four hydrogen atoms because the valence of carbon is 4 and that of hydrogen is 1. This compound, which has the molecular formula of CH_4, is known chemically as methane. It, being the simplest hydrocarbon, will be used to illustrate the carbon atom as a three-dimensional figure. The comprehension of this concept is necessary for the full understanding and appreciation of the meaning of the conventional formula of methane.

In a few compounds not commonly encountered, carbon exhibits a valence of 2 or 3. A discussion of the evidence for the existence of these unusual valences of carbon can be found in advance treatises, such as that edited by Gilman (see references at the end of the chapter).

The four valences of carbon are equal. If they were not, the substitution of one hydrogen atom by some other element or group would yield different compounds, depending on which hydrogen was replaced. In order to illustrate the three-dimensional aspects of the compounds of carbon, the carbon atom can be pictured as located at the center of a sphere from which the four valences radiate in such a way as to divide the surface of a sphere equally. Under these circumstances, the angle between the valences is 109° 28′. This arrangement for the methane molecule is illustrated by I in Fig. 12. If straight lines are drawn through the points where the valence lines intersect the surface of the sphere, a solid figure with four equal faces, a regular tetrahedron, will be formed. The concept of the carbon atom, located at the center of a regular tetrahedron with its four valences directed toward the corners (II of Fig. 12), is used widely to show the spacial relationship of groups in special types of organic compound, which will be discussed later.

While I of Fig. 12 is a truer representation of the actual positions of the hydrogen atoms in the methane molecule, for convenience and speed of writing the usual method of writing the graphic formula of methane is that represented by III of Fig. 12. In using this formula, the student should visualize the tetrahedral model from which it was derived, and should keep in mind that the straight lines represent pairs of shared electrons. Although actually the valence electrons of carbon are revolving in orbits, it is convenient and helpful to have a simple model for illustrative purposes. The one in which the electrons are considered as fixed at the corners of a regular tetrahedron, with the carbon atom at the center, is the model most widely used by organic chemists.

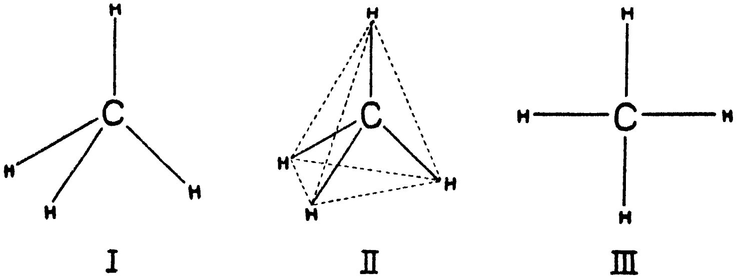

Fig. 12.—Three-dimensional aspects of the carbon atom in the methane molecule.

Saturated Aliphatic* Hydrocarbons

Methane.—It has been mentioned already that III in Fig. 12 represents the *graphic formula* for methane. This type of formula is one in which the elements or groups attached to *each* of the valences of the carbon atom are represented diagrammatically. It cannot be emphasized too strongly that the beginner should continue to use graphic formulas until he fully appreciates the fact that carbon has a valence of 4, and *until it*

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*Organic compounds often are classified into three main divisions—*aliphatic*, *aromatic*, and *heterocyclic*. Aliphatic compounds (Greek, aleiphar = fat) were given this name originally because natural fats belonged to this class. Aliphatic compounds characteristically have their carbon atoms joined in open chains while aromatic compounds have their carbon atoms in closed rings or cycles. Heterocyclic compounds are ring compounds containing carbon atoms and one or more atoms of some other element in the ring structure.

becomes habitual to check an organic formula to see that all four valences of the carbon atom are satisfied. Only when the concept of the quadrivalence of carbon has become firmly fixed in mind is it permissible to use the shorter, molecular formulas, such as CH_4.

Occurrence. If one rows into a swamp or marsh where there is considerable fallen vegetation and remains quiet for a time, he will observe bubbles rising to the surface. In some cases, where a large amount of this gas is being evolved, it actually can be lighted with a match. This gas, which is methane, is formed by the slow decomposition of vegetable matter in the absence of oxygen, and, because of its occurrence in marshes, it is known also as "marsh gas." In addition, methane is found in coal mines, where it became entrapped during the formation of the coal. Geologists tell us that our present coal deposits were formed from luxuriant vegetation that grew on the earth in prehistoric times, and it seems probable that methane was an accompanying substance formed during the same process. When the coal is mined, the pressure of surrounding deposits is removed, and the pockets of methane are released. The gas often forms explosive mixtures with the air. For this reason, coal miners refer to it as "firedamp." Hence, this simplest hydrocarbon is known variously as methane, marsh gas, or firedamp. Such a multiplicity of names for a single substance is a common occurrence in organic chemistry.

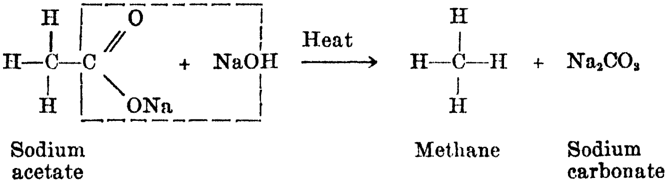
Under certain conditions the bacteria of the lower intestinal tract form methane from undigested carbohydrates; at times it may constitute as much as 50 per cent of the intestinal gases. Some years ago a group of scientists determined that a quantity of methane and hydrogen that would be sufficient to keep a small flame burning day and night was formed in the intestinal tract of a cow. At sewage disposal plants microbiological fermentation of the sludge yields methane which is used for fuel in some cases.

By using a spectroscope to break up the light waves reaching the earth from another planet, astrophysicists have found that

Neptune, with a surface temperature of -200° C., has clouds composed of methane snow.

Methane is the most abundant of the gaseous hydrocarbons. The percentage of methane in natural gas varies from 60 to 98 per cent, but ordinarily it is about 90 per cent methane. According to the Bureau of Mines, the total marketed production of natural gas for the year 1945 amounted to 3,875,000,000 cu. ft. of which 15.6 per cent was used for domestic fuel and heating purposes.

Preparation. Methane can be prepared in the laboratory by heating sodium acetate with a strong alkali in the absence of water. This is a general method for preparing hydrocarbons of the methane series. In each case the hydrocarbon formed contains one less carbon atom than the number of carbon atoms contained in the salt of the organic acid used. This results because one carbon atom of the acid is needed for the formation of sodium carbonate:



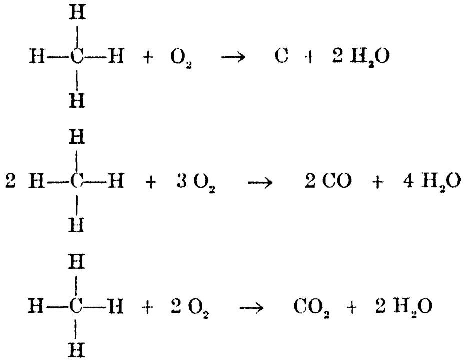
In practice, soda lime (a mixture of sodium hydroxide and calcium oxide) is used since the calcium oxide reduces the action of the sodium hydroxide on the glass vessel.

Physical properties. Physical properties are those, such as boiling point, melting point, and solubility, that can be determined without bringing about any chemical change in the composition of the substance.

Methane is practically insoluble in water (5 cc. in 100 cc.); therefore, it can be collected over water. It is a colorless, odorless gas, and has a melting point of -182.6° C. Accordingly, under all ordinary circumstances methane is encountered in the gaseous state.

Chemical properties. The most characteristic chemical property of methane is that of inertness or nonreactivity. It is on account of this property that the class of hydrocarbons, of which methane is a member, is known as the paraffin hydrocarbons. The name paraffin is derived from two Latin words, *parum* and *affinis,* meaning "little affinity."

The most important reaction of methane is that of burning or combustion (oxidation). This is illustrated by the following series of equations:



$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}H} + O_2 \rightarrow C + 2\,H_2O$$

$$2\,\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}H} + 3\,O_2 \rightarrow 2\,CO + 4\,H_2O$$

$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}H} + 2\,O_2 \rightarrow CO_2 + 2\,H_2O$$

It may well be emphasized at this point that any hydrocarbon on *complete* combustion in the presence of a sufficient supply of oxygen yields only carbon dioxide and water. In an equation for the complete combustion of *any* hydrocarbon, the final products are carbon dioxide and water, and the equation must be balanced; for, according to the law of conservation of mass, matter can be neither created nor destroyed. In other words, the same number of atoms must appear on each side of the arrow. When insufficient oxygen is present, or when conditions are not favorable for complete oxidation, other products, such as carbon or carbon monoxide, are formed, as is illustrated by the foregoing equations. This explains why it is dangerous to run the engine of an automobile in a closed garage. Gasoline is made up of hydrocarbons of the same class as methane, and, when the engine is cold, complete combustion does not take place. As a result, carbon monoxide is formed (see above). This acts as a poison by combining with the hemoglobin of the blood (see page 591).

Another important type of reaction that methane undergoes is halogenation. In the presence of sunlight or ultraviolet light and at its boiling point, methane will react with the halogens, chlorine and bromine, to give halogen derivatives. These compounds will be considered later.

Uses. As might be expected for an inexpensive organic compound of such wide distribution, methane has many uses. One of its most important uses is as a fuel for both domestic and industrial purposes. The annual consumption of natural gas is equivalent in fuel value to 100,000,000 tons of coal or about 500,000,000 barrels of fuel oil. Large quantities of methane (431,830,000,000 cu. ft. in 1945) are used for the production of the carbon black or lampblack used as a filler in rubber tires. In 1945 domestic sales of carbon black to rubber companies amounted to 804,386,000 pounds or 95 per cent of domestic sales. The ink and paint trades are the other large consumers of carbon black. Methane is burned in the presence of an insufficient amount of oxygen, the surface of the combustion chambers (on which is deposited the carbon black) being cooled by water sprays.

Fig. 13.—A carbon black plant producing 15,000,000 pounds annually by the incomplete combustion of natural gas (mostly methane). Mixing of one part carbon black to two parts crude rubber increases the wearing qualities of the product fourfold. Carbon black is used also in lacquers and inks, such as that used to print this page. (Courtesy of the Godfrey L. Cabot Co., Inc.)

The newest use of methane is for the synthesis of gasoline by the Fischer-Tropsch process. The American modification of this process uses an inexpensive iron-containing catalyst in the controlled combustion of methane with pure oxygen. The products are carbon monoxide and hydrogen, which are used for the synthesis of high quality gasoline and oxygen-containing compounds such as alcohols.

✓**Homologous Series.**—Methane is the first member of an homologous series. *An homologous series is a group of similar compounds whose formulas differ by a constant amount,* usually CH_2. The members of such a series are known as *homologues.* The homologous series to which methane belongs is known variously as the paraffin, saturated, or methane series. In the case of any homologous series, it is possible to write a general formula for the group from which the molecular formula of any individual member can be obtained if its number of carbon atoms is known. For the paraffin series, this general formula is C_nH_{2n+2}, where *n* represents the number of carbon atoms in the molecule. The names and molecular formulas of the first twenty members of the paraffin series are shown in Table V. The molecular formula of an organic compound, in contrast to the graphic formula, shows only the kind and total number of atoms in a molecule, and indicates nothing whatsoever of their spatial relationships.

As a *minimum* requirement, the names and corresponding number of carbon atoms of each of the first ten members of this series should be memorized. Generally, the subject matter of organic chemistry should *not* be memorized: it should be understood; but the above is one instance where the material should become as familiar as the multiplication tables. The reason for this soon will become evident. In the first place, the names of the common organic radicals can be obtained easily from the names of the compounds in the paraffin series. *A radical can be defined as a group of atoms that passes through a reaction unchanged.* Familiar examples from inorganic chemistry are the sulfate ($-SO_4$), nitrate ($-NO_3$), and ammonium ($-NH_4$) radicals. The names of the common organic radicals can be obtained by dropping the *-ane* ending of the hydrocarbon name and

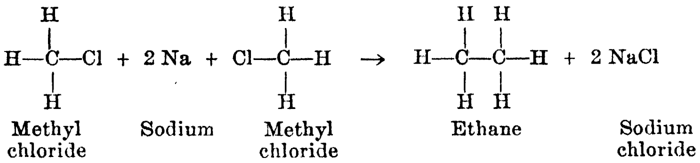
TABLE V

PHYSICAL CONSTANTS OF PARAFFIN HYDROCARBONS

MOLECULAR FORMULA	NAME	MELTING POINT °C.	BOILING POINT °C.	NAME OF ALKYL RADICAL	FORMULA OF ALKYL RADICAL
CH_4	Methane	-184.0	-161.5	Methyl	CH_3-
C_2H_6	Ethane	-172.0	- 88.3	Ethyl	C_2H_5-
C_3H_8	Propane	-189.9	- 44.5	Propyl	C_3H_7-
C_4H_{10}	Butane	-135.0	0.6	Butyl	C_4H_9-
C_5H_{12}	Pentane	-131.5	36.2	Pentyl (Amyl)	$C_5H_{11}-$
C_6H_{14}	Hexane	- 94.2	69.0	Hexyl	$C_6H_{13}-$
C_7H_{16}	Heptane	- 90.0	98.4	Heptyl	$C_7H_{15}-$
C_8H_{18}	Octane	- 56.5	124.6	Octyl	$C_8H_{17}-$
C_9H_{20}	Nonane	- 51.0	150.6	Nonyl	$C_9H_{19}-$
$C_{10}H_{22}$	Decane	- 32.0	174.0	Decyl	$C_{10}H_{21}-$
$C_{11}H_{24}$	Undecane	- 26.5	194.5	Undecyl	$C_{11}H_{23}-$
$C_{12}H_{26}$	Dodecane	- 12.0	214.5	Dodecyl	$C_{12}H_{25}-$
$C_{13}H_{28}$	Tridecane	- 6.2	234.0	Tridecyl	$C_{13}H_{27}-$
$C_{14}H_{30}$	Tetradecane	5.5	252.5	Tetradecyl	$C_{14}H_{29}-$
$C_{15}H_{32}$	Pentadecane	10.0	270.5	Pentadecyl	$C_{15}H_{31}-$
$C_{16}H_{34}$	Hexadecane	20.0	287.5	Hexadecyl	$C_{16}H_{33}-$
$C_{17}H_{36}$	Heptadecane	22.5	303.0	Heptadecyl	$C_{17}H_{35}-$
$C_{18}H_{38}$	Octadecane	28.0	317.0	Octadecyl	$C_{18}H_{37}-$
$C_{19}H_{40}$	Nonadecane	32.0	330.0	Nonadecyl	$C_{19}H_{39}-$
$C_{20}H_{42}$	Eicosane	38.0	----	Eicosyl	$C_{20}H_{41}-$

adding *-yl*. For example, the radical corresponding to methane is methyl (CH_3-); ethane becomes ethyl (C_2H_5-), etc. Collectively, these radicals derived from the paraffin hydrocarbons are known as the *alkyl radicals*. It would be advisable for the student to write out the names of the radicals corresponding to the various hydrocarbons of the saturated series through decane, and to drill himself on these until they become firmly fixed in mind. Learning the names of the various radicals and their corresponding number of carbon atoms is of utmost importance, because these names will be used continually during the study of organic chemistry. Furthermore, this information should not be learned only in one order (methyl, ethyl, propyl, etc.). The student should practice until the name butyl, for instance, brings to mind instantly the association of four carbon atoms, or vice versa.

Ethane.—The second member of the paraffin series is known as ethane. It is composed of 2 carbon atoms and 6 hydrogen atoms. It occurs in natural gas in amounts varying from 1 to 10 per cent. The compound can be prepared in the laboratory by the action of sodium on methyl chloride.



$$\underset{\text{Methyl chloride}}{H-\overset{H}{\underset{H}{\overset{|}{\underset{|}{C}}}}-Cl} + \underset{\text{Sodium}}{2\,Na} + \underset{\text{Methyl chloride}}{Cl-\overset{H}{\underset{H}{\overset{|}{\underset{|}{C}}}}-H} \rightarrow \underset{\text{Ethane}}{H-\overset{H}{\underset{H}{\overset{|}{\underset{|}{C}}}}-\overset{H}{\underset{H}{\overset{|}{\underset{|}{C}}}}-H} + \underset{\text{Sodium chloride}}{2\,NaCl}$$

This is known as the Wurtz reaction or synthesis, since it was first carried out by Charles A. Wurtz, a French chemist. Many reactions in organic chemistry are "name" reactions; however, only a few of the most frequently used ones will be given in our discussions.

Ethane, like methane, is a colorless, odorless gas, only slightly soluble in water and relatively inert. Its principal reaction is that of combustion, but under special conditions it can be made to react with halogens and with nitric acid.

It is not merely by chance that the properties of ethane are so similar to those of methane. It is a characteristic property that all the members of a particular homologous series have similar chemical properties.

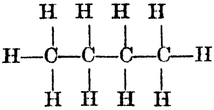
Propane.—The three-carbon homologue of methane, propane, occurs in natural gas as it issues from the well and also in the gaseous by-products of petroleum refining. It is a colorless, odorless gas, slightly soluble in water, and can be prepared in the laboratory by the Wurtz synthesis, although laboratory preparation is not usually employed since other sources are so much cheaper. Recently, mixtures of propane and ethane have been subjected to conditions of high temperature and pressure to produce ethylene, which is used in the synthesis of one of the synthetic rubbers and in the production of ethyl alcohol.

Butane, Pentane, and Other Saturated Hydrocarbons.—Butane C_4H_{10}, and pentane, C_5H_{12}, are obtained from natural gas, the gaseous by-products of petroleum refining, and from casing head gas (so-called because it collects at the top of casings in oil wells).

The preparation, occurrence, and the physical and chemical properties of the higher members of this series will not be dealt with in detail, because they have properties very similar to those of the homologues already discussed. The fact that homologues are similar in many of their properties obviates the necessity of the student's memorizing a whole mass of information; instead, if he knows the characteristics of one or two key members of a series, he can reason out much of the information about the other members. To illustrate, all members of the paraffin series are chemically inert, their principal reaction being that of combustion, although under certain conditions they can be made to react with halogens and with nitric acid. In addition, they are insoluble in water and soluble in organic solvents. However, there are exceptions to the general principle of the similarity of homologues due to differences in the ways in which the carbon atoms are linked together, and the student is cautioned to watch for these exceptions.

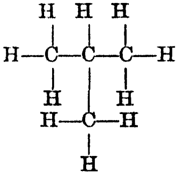
In general, it can be said of the physical properties of a homologous series that with increasing molecular weight, there is a corresponding increase in boiling point and specific gravity.* This is illustrated by the fact that the first four members of the methane series are gases, the next thirteen are liquids, and the higher homologues are solids at ordinary temperature and pressure. This general rule also has some exceptions, and it, too, must be applied with reservations.

Isomerism.—We have seen that the four-carbon homologue of methane (butane) has the molecular formula C_4H_{10}. This is the first case we have considered in which there is more than one compound with the same molecular formula. The graphic formulas of butane show that there are two possible combinations.



$$\begin{array}{cccccc} & H & H & H & H & \\ & | & | & | & | & \\ H- & C- & C- & C- & C- & H \\ & | & | & | & | & \\ & H & H & H & H & \end{array}$$

n-Butane



Isobutane

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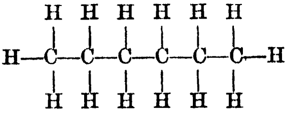
*Specific gravity is the ratio of the weight of a substance to the weight of an equal volume of water at 4° C.

This phenomenon of two or more compounds having the same molecular formula, but possessing different physical and chemical properties, is known as isomerism. The compounds themselves are known as *isomers.* The subject of isomerism is a very important one, for isomers are encountered continually in organic chemistry. The necessity of having available some means of distinguishing between isomers emphasizes the importance of graphic formulas, which show the spacial relationship of the carbon atoms as well as the mode of linkage of the various atoms in the molecule. The existence of isomers is somewhat analogous to the fact that with a given amount of mortar and a given number of bricks many different types of houses can be built.

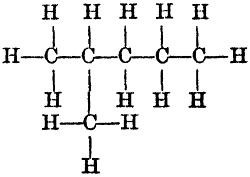
The type of isomerism illustrated by butane is known as *chain* or *nuclear* isomerism, because the differences occur in the linkages in the carbon chain. As the number of carbon atoms in a compound increases, the number of isomers increases at a rapid rate. For example, the six-carbon homologue has five isomers, whereas there are 75 different compounds having the molecular formula $C_{10}H_{22}$.

Nomenclature.—It must be evident by now that the simple system of nomenclature (used above for butane) in which the isomer with the carbons linked in a continuous chain is termed the *normal,* usually abbreviated as *n-,* and in which the branched-chain form is termed *iso-,* will be inadequate for instances in which there are more than two isomers. To meet this need, and also to decide on a uniform system of naming organic compounds, a meeting of organic chemists was held in Geneva, Switzerland, in 1892. The system devised was modified and simplified somewhat by the International Union of Chemistry, which met at Liege in 1930. According to this latter system (the "I.U.C. system"), a compound is named as a derivative of the hydrocarbon corresponding to the *longest, continuous carbon chain.* Where there is branching of the carbon chain, the name is modified according to the kind and position of the groups attached to the longest, continuous carbon chain. The chain is numbered from the end nearest the branching, and the position of the alkyl or other groups attached is indicated by numbers.

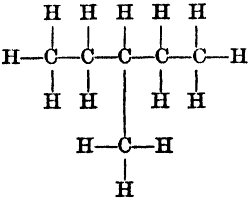
Just as a house number indicates the relative location of the house in the block, so the numbers in the I.U.C. system indicate the position of the groups attached to the carbon chain. To illustrate how the system works, let us write the formulas and names of the isomers of hexane, C_6H_{14}.



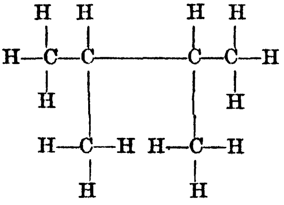
n-Hexane



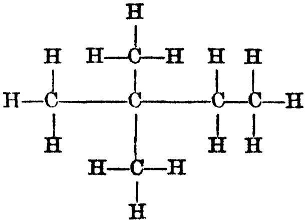
2-Methylpentane



3-Methylpentane



2,3-Dimethylbutane



2,2′-Dimethylbutane*

In order that the student will become familiar with the I.U.C. system of nomenclature, he should write out the graphic formulas of all the possible isomers of heptane (nine isomers). This does not mean that the longest, continuous chain in all the isomers will contain 7 carbon atoms; it does mean, however, that there will be 7 carbon atoms and 16 hydrogen atoms in each isomer.

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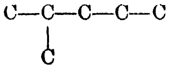
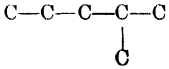
*An early system of nomenclature, still used somewhat, names hydrocarbons as derivatives of methane. The most highly substituted carbon atom is taken as the methane carbon. For example, 2, 2 dimethylbutane would be named trimethylethylmethane.

The student should avoid the error of placing a carbon below the end carbon in a horizontal chain in the belief that this represents a branch. It should be borne in mind that the representation of a compound on a flat surface, such as a sheet of paper, is inadequate, since molecules actually possess three dimensions in space. Even though the carbon atoms usually are written in a straight line, it must not be thought that the bonds between the atoms are like rigid, steel wires; rather, they should be thought of as similar to rubber bands which may be bent in various directions at will, still leaving the carbon atoms in a continuous chain.

Another error often made by the uninitiated is in assuming that the following formulas represent two isomers:



$$\begin{array}{ccccccccc} C & - & C & - & C & - & C & - & C \\ & & | & & & & & & \\ & & C & & & & & & \end{array}$$



$$\begin{array}{ccccccccc} C & - & C & - & C & - & C & - & C \\ & & & & & & | & & \\ & & & & & & C & & \end{array}$$

These really are formulas of the same compound; the one carbon side chain is attached to the first carbon from the end of the longest continuous chain in both cases; they are only two ways of representing the same thing.

Petroleum.—Since the principal source of the aliphatic hydrocarbons is petroleum, and since petroleum refining is one of the chief industries on which our civilization is based, it is appropriate that this substance be considered in some detail. The term petroleum often is used to include both gaseous and liquid hydrocarbons of mineral origin. Thus, natural gas, natural or casing-head gasoline, and crude petroleum are covered by this term.

Crude petroleum, which is a brown to greenish-brown liquid, known more romantically as black gold, is a source of lubrication and fuel for passenger cars, buses, and trucks, and of domestic fuel, and a source of raw materials for the manufacture of over a hundred different organic compounds. There is hardly an activity in our everyday lives that is not affected directly or indirectly by the products obtained from crude oil. Alcohols, glycerin, synthetic rubber, and explosives are only a few of the many products that today are made partly or entirely from petroleum. The value of America's annual production of petroleum exceeds that of any of our minerals.

Striking advances have been made in the petroleum industry since Colonel Edwin L. Drake, drilling near Titusville, Pennsylvania, in August, 1849, found, on returning to work one morning, that the well he had drilled to a depth of 59 feet had filled up with oil overnight. Since that time, thousands of wells have been drilled. The deepest producing well is in Iberia Parish, Louisiana, which was drilled to 14,301 feet and is producing from 13,780 feet. The world's deepest well is one in west central Oklahoma at 17,008 feet. This is indicative of a belief among oil men and geologists that quantities of hydrocarbons will be discovered at depths of 15,000 to 20,000 feet.

Occurrence. Petroleum is very widely distributed, but the United States produces about 60 per cent of the world's supply of crude oil. Other large oil-producing regions, in the order of quantity of crude oil produced in 1946, are Venezuela, Russia, Iran, Arabia, and Mexico. Largest reported reserves of petroleum are in Arabia and Iran. In 1946 the oil production of the United States amounted to 1,748,772,000 barrels of 42 gallons

TABLE VI

PRODUCTION OF CRUDE PETROLEUM BY STATES*

STATE	1946 PRODUCTION (THOUSANDS OF BARRELS)	PER CENT OF TOTAL
Texas	764,593	43.7
California	316,606	18.1
Louisiana	151,608	8.7
Oklahoma	137,228	7.8
Kansas, Missouri, and Nebraska	96,579	5.5
Illinois	74,613	4.3
Wyoming	38,544	2.2
New Mexico	36,704	2.1
Arkansas*	28,099	1.7
Mississippi	24,248	1.4
Michigan	17,138	1.0
Pennsylvania	13,057	0.7
Colorado	11,591	0.7
Montana	9,029	0.5
Other states	29,135	1.6
U. S. Total	1,748,772	100.0

*Statistics from Oil and Gas Journal 45: 151, 1947.

each. The quantities of oil produced by the different states in 1946 are shown in Table VI.

Origin. A number of theories that attempt to explain the origin of petroleum have been advanced. The most plausible theories can be divided into two groups: *inorganic* and *organic.* In the inorganic theory, the assumption is made that petroleum was formed by the action of water on metallic carbides. On the basis of this theory, it is supposed that early in the history of this planet temperatures as high as that of the electric furnace (about 3,000° C.) existed. At such temperatures, metallic carbides, such as those of calcium and iron, were formed, and, when these compounds came in contact with water percolating down from the surface, the highly active hydrocarbon, acetylene, was formed. Under the conditions of high temperature and pressure deep in the earth, this hydrocarbon combined with itself to form petroleum. The inorganic theory seems to offer a plausible ex-

Fig. 14.—Night drilling operation in the Centralia, Ill., oil field. Heavy producing wells in this new field enabled Illinois to rise from fourteenth place among the oil-producing states in 1936 to fourth place in 1940. (Courtesy of the E. H. Brown Advertising Agency.)

planation for the petroleum found occasionally in hard, igneous rocks, and in meteors.

The inorganic theory, however, fails to offer an adequate explanation for the varied properties of different crude oils, and does not account for the presence of nitrogen and sulfur compounds. To overcome these objections, the organic theory was advanced. It assumes that petroleum arose from pre-existing plant and animal life—in other words, that the oil fields of the world today are the graveyards of trillions upon trillions of plants and animals, mainly microscopic marine and swamp organisms. At the present time we know that the sea contains an abundance of microscopic plant life, commonly referred to as plankton. Because this form of plant is microscopic in size, it is able to remain near the surface and manufacture its food from carbon dioxide and water in the presence of sunlight. Hence,

Fig. 15.—Signal Hill oil field in southern California. The location of the derricks indicates the size of the field and the number of derricks indicates the enormous quantity of oil that must have collected in the underground pool. From the standpoint of conserving the nation's oil supply, the picture illustrates the opposite of the desirable procedure. A few wells uniformly distributed over the field would produce a much larger yield of oil at lower production costs. (Courtesy of the Spence Air Photos, Los Angeles, Calif.)

according to this theory, in past geological ages "organic muds" found in shallow inland seas, and formed principally from the microscopic plant and animal life, were covered by thousands of feet of mud and sand from subsequent geological epochs. The inorganic parts of the earlier deposits were transformed into dense shales and sandstone, while the pre-existing plant and animal forms were changed under the conditions of high temperature and pressure into petroleum. The collection of petroleum into pools is thought to have taken place as a result of the pressures which formed the alluvial muds into shales, at the same time forcing the oil into the more open and less compressible sands. Water movements in the underground strata also may have tended to flush the oil before them, so that the petroleum accumulated at the tops of folded rocks or in vast sand beds in pools, ranging in size from a few acres to 40 or 50 square miles in extent.

Obviously, it is difficult to prove absolutely any theory of the origin of petroleum by laboratory methods, because it is impossible to equal in the laboratory the geological timetable or the effects of temperature and pressure deep in the earth, which metamorphosed the original material into petroleum during countless ages. The theory of the organic origin of petroleum seems best to account for the varied properties of different crude oils. Each theory proposed has some degree of plausibility, and it is probable that all the processes thus far postulated operated to a certain extent during the formation of petroleum.

Oil well production. As is illustrated in Fig. 15*A* (page 82) by the diagram of an oil well, petroleum is found as pools at the top of arches of folded sedimentary rocks. In some cases when the overlying rock is pierced by the drill, the pressure of accompanying gas is so great that the oil is forced to the surface with such pressure that a "gusher" results. More commonly, the pressure of the gas merely causes the oil to flow through pipes attached to the casing. The gas pressure in all wells finally decreases to the point where the oil must be pumped to the surface.

The authorities agree that our supply of petroleum is not inexhaustible, but there is disagreement as to how long it will last. During the recent war we consumed our reserves at a prodigious rate and it is most important to our national security that we conserve our endowment of petroleum. It has been estimated that for each barrel of crude oil brought to the surface, three are left underground. Hence, one method of increasing our supply is to develop better methods of oil recovery from underground reserves.

Several improvements in the recovery of oil have been made in the past twenty-five years. One of these is the reintroduction under high pressure of natural gas to the wells. In one field the reintroduction of natural gas under a pressure of 1,400 pounds per square inch and a slower rate of pumping doubled the amount of oil that would have been recovered by older methods of production.

Another means of improving recovery is by water flooding through a central well and allowing water to extend gradually outward in an expanding circle, thus driving oil into surrounding wells. Acid treatment of oil-bearing limestone formations has become an accepted procedure. It is estimated that over 25,000,000 gallons of hydrochloric acid are used annually for this purpose. The acid contains an inhibitor, such as a tertiary amine, to reduce corrosion on iron equipment to a minimum. Oil wells also are shot with nitroglycerine. This results in added oil production because of the increased drainage from fissures and cracks.

Natural gasoline. The gas found in most wells, which forces the liquid petroleum to the surface in many cases, contains considerable quantities of the more volatile components of the oil. These must be removed before the natural gas can be sent through pipe lines or they will condense in the pipes and interfere with gas transportation. This condensate is known as natural or casing-head gasoline. It is absorbed by passing the well gases through a low boiling oil obtained from the distillation of petroleum. The natural gasoline is then recovered by heating the oil. Natural gasoline is blended with refinery products to make for greater ease in starting in motor fuels.

Liquified petroleum gases. Propane and butane are the principal products included in the commercial term, liquified petroleum gases. They are absorbed in the same heavy oil as natural gasoline, but at ordinary temperature and pressure they are too volatile to be retained in the gasoline. Commercially, however, they are compressed and marketed as a liquid; hence the term, liquified petroleum gases.

It is estimated that in 1946 the marketed production of liquefied petroleum gases was 1,425,000,000 gallons. The use of these gases as domestic fuel in rural areas has increased at a spectacular rate during the past decade. A factor in the increased production of liquefied petroleum gases has been their increased use by gas utility companies for the enrichment of natural gas and as stand-by reserves to maintain pressure at peak load periods.

From the standpoint of quantities consumed, next to their use as fuels, the most important use of the liquefied gases is as raw materials for chemical manufacture. Propane is used to a greater extent than any of the others in the manufacture of *nitroparaffins.* In this process, which has become commercially important since 1940, nitric acid vapors heated to 400° to 450° C. are mixed with the gaseous paraffin hydrocarbon under pressure of about 150 pounds per square inch. The nitration takes place almost instantly and the products are rapidly cooled to prevent oxidation. The nitration of propane gives a variety of products, the principal ones of which are: nitromethane, CH_3NO_2; nitroethane, $CH_3CH_2NO_2$; 1-nitropropane, CH_3CH_2-CH_2NO_2; and 2-nitropropane, $CH_2CH(NO_2)CH_3$. The nitroparaffins are excellent solvents for a host of materials. In cellulose acetate lacquers they assure good flow and rapid hardening properties. They are unusually more effective than ordinary solvents as paint and varnish removers. They are the starting materials for so many chemical syntheses that they may become the basis of a new branch of chemical industry.

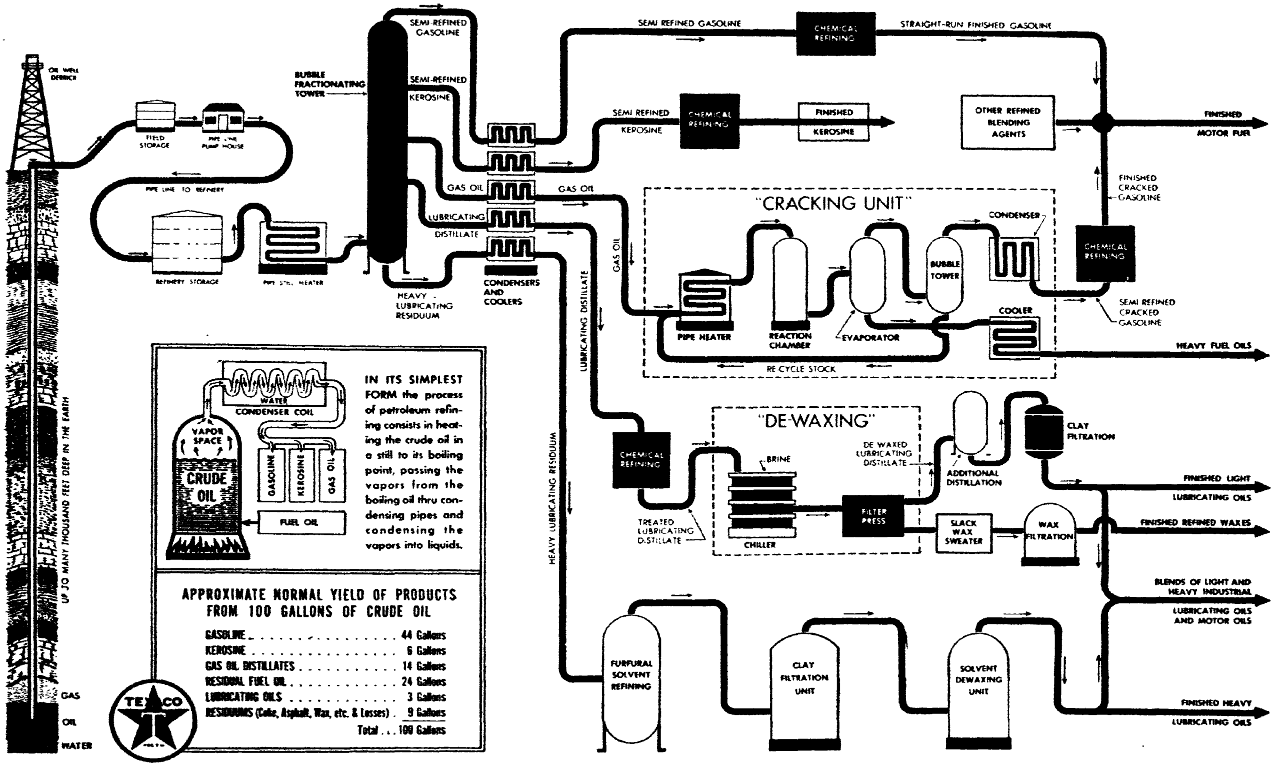
Another one of the liquefied petroleum gases, butane, is added to motor fuels in the winter to increase their volatility and hence their ease of starting. Butane also is used in making aviation gasoline and butadiene, an important product in the manufacture of synthetic rubber. Without these two products our war effort would have been seriously crippled.

Products of refining. Most products obtained from petroleum are separated by the process known as fractional distillation. Distillation involves two physical changes: *vaporization* followed by *condensation.* Vaporization of any liquid takes place when molecules at the surface of the liquid have received enough extra energy in the form of heat to cause them to leave the surface and thus be transformed into the gaseous state. Condensation of the vapor to a liquid results when some of the energy of the gaseous molecules is given up to the cooler walls of the container known as the condenser.

The distillation of petroleum differs from the distillation of water in that crude oil is a mixture instead of a pure substance. Different compounds vaporize as the temperature of the crude oil increases. As the petroleum in the still is heated, the substances with the lowest boiling points come off first. Those that boil within a given range of temperature are collected together in one receiver, and are known as a fraction. In the case of petroleum, these fractions consist of a mixture of compounds with boiling points and other physical properties characteristic of closely related homologues. In fact, these physical properties are related closely enough to enable the fractions to be used for one purpose.

The principal fractions separated from petroleum include petroleum ether, gasoline, napthas, kerosene, light fuel oils, gas oil, heavy fuel oil, light lubricating oil fraction, waxes, heavy lubricating oil fraction, and a residue that may consist of asphalt or coke. The division of fractions does not follow strict rules. It depends upon the demand at a particular refinery, and the type of petroleum stock being used. An outline of the steps in the separation of petroleum into useful products is presented in Fig. 15*A*.

Uses of petroleum fractions. The fraction separated from petroleum that has the boiling point range of 30° to 60° C. is known as petroleum ether. It is used as a solvent, especially in the chemical laboratory, for the quantitative extraction of fats and oils from various natural materials.



IN ITS SIMPLEST FORM the process of petroleum refining consists in heating the crude oil in a still to its boiling point, passing the vapors from the boiling oil thru condensing pipes and condensing the vapors into liquids.

APPROXIMATE NORMAL YIELD OF PRODUCTS FROM 100 GALLONS OF CRUDE OIL

GASOLINE	44 Gallons
KEROSINE	6 Gallons
GAS OIL DISTILLATES	14 Gallons
RESIDUAL FUEL OIL	24 Gallons
LUBRICATING OILS	3 Gallons
RESIDUUMS (Coke, Asphalt, Wax, etc. & Losses)	9 Gallons
Total	100 Gallons

Fig. 15A.—Petroleum refinery flow chart, tracing crude oil from well to finished products. The usual order of the steps in the separation of crude oil into various useful products is presented graphically in the above diagram. The value of America's annual production of petroleum exceeds that of any of our minerals. (Courtesy of the Texas Company.)

Gasoline is the fraction containing a mixture of hydrocarbons from pentane to dodecane, and having a boiling point range of 80° to 200° C. It is the distillate that furnishes power for the nation's motor cars, and is the one for which there is the greatest demand.

Potentially, gasoline contains enormous quantities of energy. A gallon contains enough energy so that if it were entirely utilized, it would lift a weight of nine tons to a height of one mile. The energy in a gallon of gasoline is sufficient to propel a car 450 miles if all the energy could be utilized for driving the car. The internal combustion engine, however, is not a very efficient utilizer of this potential power. Only about 25 per cent of the energy of gasoline is used to move the car; the remainder escapes as heat through the exhaust, is lost as heat through the radiator, and is used to overcome friction.

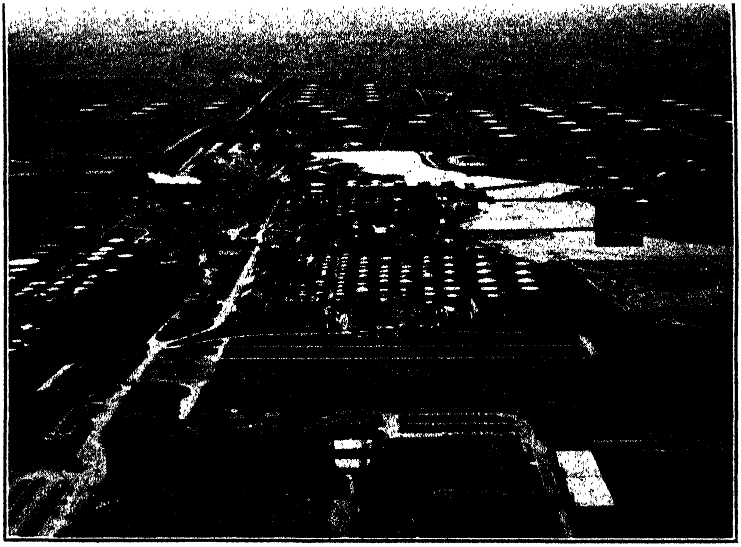


Fig. 16.—Refinery of Continental Oil Company, Ponca City, Okla., where more than 450 petroleum products are manufactured. The plant has a daily capacity of more than a million gallons of crude oil and 750,000 gallons of gasoline. In the background is a part of the 422,000,000 gallon tank farm. (Courtesy of the Continental Oil Company.)

By the term naphtha is meant a product having properties intermediate between gasoline and kerosene. Often cleaner's naphtha has a boiling point range of 90° to 140° C. It is used extensively for dry cleaning. Usually enough chlorinated hydrocarbons, such as carbon tetrachloride or trichloroethylene, are added to reduce the fire hazard that would exist if naphtha alone were employed.

The fraction boiling between 200° and 300° C. is known as kerosene. In addition to the use of kerosene for fuel and illuminating purposes, other products like light Diesel fuel oil and absorbent oil for natural gasoline are prepared from it.

Gas oil is a rather indefinite term applied to fractions having boiling point ranges intermediate between those of kerosene and lubricating oils. Its chief use is to produce additional gasoline by a process that is known as cracking. This process will be discussed later. Large quantities of gas oil are used for domestic heating and as fuel for Diesel engines.

The lubricating oil fraction is usually considered to include all the volatile material obtained after the gas oil has been removed. This fraction of petroleum is made into hundreds of products, such as medicinal oils (Nujol), emulsified spray oils, transformer oils, motor oils, printing ink oils, etc.

Solvent refining, especially of the lubricating oil fraction of petroleum, is becoming increasingly important. This procedure consists in (1) mixing the petroleum fraction with a suitable solvent that preferentially dissolves the undesired component, (2) separating the resulting two layers, and recovering the solvent by distillation. Solvents used for this purpose include furfural, Chlorex, phenol, and a mixture consisting of liquid propane and cresylic acid.*

Petroleum is sometimes classified as having a paraffin or an asphalt base depending on the relative amounts of these two substances obtained from the crude oil. On cooling the lubricating oil fraction in paraffin base oils, paraffin wax separates and is removed in filter presses. This wax is used for home canning, coating paper, making candles, in chewing gum, in match manufacture, and for electrical insulation.

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*For an extended discussion, the reader is referred to: "Chemical Refining of Petroleum," V. A. Kalichevsky and B. A. Stagner, Reinhold Pub. Co., New York, 1942.

Other oils do not have a paraffin base, but instead yield a black, pitchlike material called asphalt. The residue of asphalt is used in the preparation of roofing materials, in waterproofing porous materials, for road building, etc.

The oils produced in the Eastern fields of the United States are, as a rule, paraffin base oils. The petroleum from the Western oil fields usually leaves a residue of asphalt. The crude oils from the mid-continental fields may be of one of the other type, or they may yield a mixture of paraffin and asphalt.

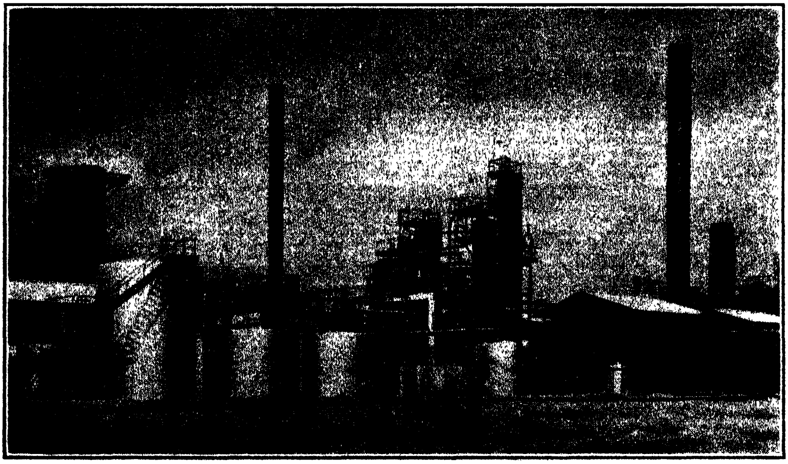


Fig. 17.—Solvent refining unit. Propane and a mixture of phenol and cresylic acids are used as solvents to remove from lubricating oils undesirable products that would later cause the formation of sludge in the crankcase. (Courtesy of the Standard Oil Company of California.)

Cracking of petroleum. With the increased number of automobiles and the corresponding rise in the demand for gasoline, the quantity of this fraction that could be obtained from crude oil by distillation was too small to meet the demand. Moreover, there were not a sufficient number of uses for the remaining fractions. Mainly because of this situation, the cracking process was developed. *Thermo-cracking* is based on the decomposition of the higher molecular weight hydrocarbons under conditions of high temperature and pressure. Gas oil and kerosene are decomposed to products within the boiling point range of gasoline. Thermo-cracking differs from distillation, which is merely a physical change, in being an actual decomposition or breaking up of the molecule. In the year 1936 the production of gasoline by the cracking process first surpassed that obtained by straight distillation. Briefly, the functions of the cracking process can be listed as follows:

1. To increase the yield of gasoline from petroleum by converting part of the high-boiling fractions into that material. In 1940 the yield of gasoline from crude oil by straight distillation was 20 per cent. If this had been the only source of gasoline, 1,444,789,000 *more* barrels of crude oil would have been necessary to supply the demand for gasoline. It has been estimated that gasoline yields of 70 to 85 per cent can be obtained from crude oil by the cracking process.

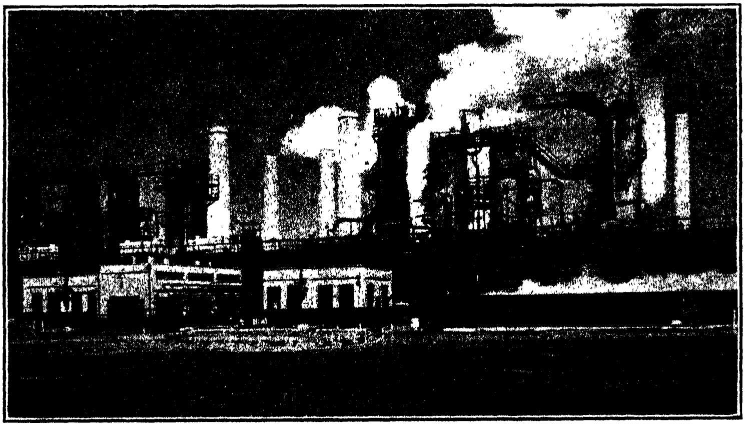


Fig. 18.—Cracking stills of a petroleum refinery. In this maze of towers and pipe lines, gasoline is manufactured from high molecular weight hydrocarbons that ordinarily would have boiling points higher than those of compounds in gasoline. In addition to yielding a high-grade gasoline, the distillate from the cracking towers contains numerous unsaturated hydrocarbons that are used in the manufacture of a number of organic products, such as ethyl alcohol and synthetic rubber. (Courtesy of the Standard Oil Company of California.)

2. To improve the quality of the gasoline. The cracking process yields compounds with a high antiknock value (see page 87).

3. To aid in maintaining a refinery stock balance by converting some of the less used products into gasoline for which there is such a large demand.

The following equations are given as a typical illustration of what might happen in the cracking still. Since the substances undergoing cracking are mixtures, the student must not conclude that these are the precise equations for the reactions involved. They are merely examples of what might happen.

$$C_{16}H_{34} \xrightarrow[\text{400-600 pounds pressure}]{\text{400-600° C.}} C_8H_{18} + C_8H_{16}$$

Hexadecane B.P. 287.5°	Octane B.P. 124.6°	Octene or octylene B.P. 126.0°

or

$$C_{16}H_{34} \xrightarrow[\text{400-600 pounds pressure}]{\text{400-600° C.}} C_{12}H_{24} + C_4H_{10}$$

Hexadecane	Dodecene B.P. 214.5°	Butane B.P. 0.6°

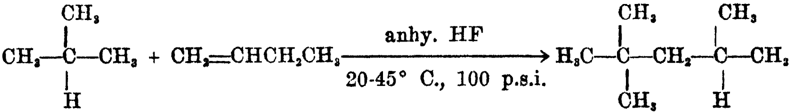
Catalytic cracking. One of the most significant recent developments in the petroleum industry is catalytic cracking. This process is superior to thermal cracking in the following respects: (1) a much wider range of transformations in molecular structure can be accomplished; (2) lower temperatures and pressures are employed and decomposition with the formation of carbon in the reaction chamber is less; (3) the octane number of the products is higher.

The *octane number* of a gasoline can be defined as the per cent by volume of isoöctane present in a mixture of this compound and n-heptane when a mixture has the same "knocking" characteristics in a special testing engine as the gasoline under examination. For example, a gasoline that has the same "knocking" characteristics as a test mixture of 75 per cent isoöctane and 25 per cent n-heptane is said to have an octane number of 75. Isoöctane was chosen as a basic testing material because of its high antiknock characteristics; *n*-heptane is one of the worst "knockers" known.

The most modern "fluid" catalytic processes employ a finely divided solid catalyst made by grinding a dried alumina-silica gel to a powder. The solid, powdered catalyst is maintained in a suspended, free-flowing condition in the reacting vapors or in the regenerating air, and thus can be handled in much the same way as a liquid. The catalyst is separated in dust recovery equipment while the products from the cracking flow to fractional distillation equipment for separation into desired components. Advantages of fluid catalytic process are that the temperature of the reaction can be controlled with exactness and that the process is essentially continuous and can be automatically controlled. The normal reactor temperatures lie in the range of 400° to 500° C. and the pressures are from 2 to 10 pounds per square inch. The products from this process have high octane numbers and need little further treatment before use for motor fuel.

Aviation gasoline. The demand for tremendous volumes of high octane aviation gasoline during World War II was primarily responsible for the development of a new hydrocarbon-chemical industry within the refining industry. The specifications for 100-octane gasoline were so exacting that a fuel meeting such requirements could not be made by ordinary refining methods. Therefore it was necesssary to blend such hydrocarbons as isopentane, neohexane, isoöctane, benzene, and substituted benzene to obtain the high qualities required in an aviation gasoline. Since most of these hydrocarbons could not be obtained from petroleum by fractional distillation methods, it was necessary to produce them by hydrocarbon conversion methods.

One of these hydrocarbon conversion methods is known as *alkylation.* The fundamental reaction is the addition of a saturated hydrocarbon to the double bond of an unsaturated hydrocarbon. Since the unsaturated hydrocarbon is thus supplied with an extra alkyl group, the process is called alkylation.



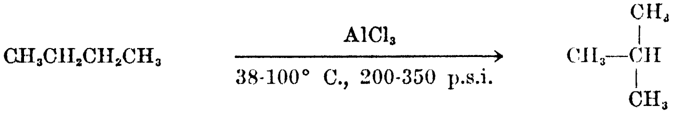
$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-CH_3 + CH_2{=}CHCH_2CH_3 \xrightarrow[20\text{-}45^\circ\text{ C., 100 p.s.i.}]{\text{anhy. HF}} H_3C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-CH_2-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-CH_3$$

2,2,4-Trimethyl pentane

Isobutane 1-Butene **Isoöctane**

The alkylation reaction takes place efficiently when liquid isobutane is agitated with anhydrous liquid hydrofluoric acid and unsaturated C_4 hydrocarbons are introduced in low (3 to 5 per cent) concentrations to the resultant emulsion.

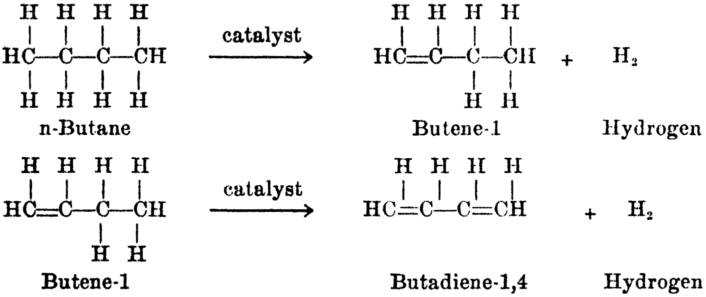
The alkylation process requires more isobutane than is normally available in natural gasoline; so another hydrocarbon conversion process known as *isomerization* was developed. In this process a rearrangement of the carbon atoms in the molecules is brought about without a change in the size of the molecule.



$$CH_3CH_2CH_2CH_3 \xrightarrow[38\text{-}100^\circ\ C.,\ 200\text{-}350\ p.s.i.]{AlCl_3} CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{CH}}}}$$

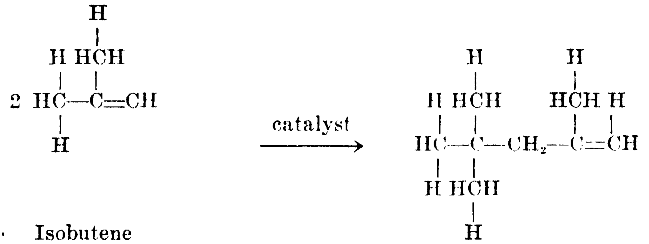
n-Butane Isobutane

In addition to their use in alkylation processes, unsaturated hydrocarbons were found essential in the production of butadiene needed for the manufacture of the most important type of synthetic rubber. Unsaturated hydrocarbons are available from the various cracking processes, but in many instances are not the right type nor present in the desired proportion. Once again the petroleum chemist used the plentiful normal butane and a process known as *dehydrogenation.* This involves the removal of hydrogen atoms from adjacent carbon atoms without breaking any carbon-to-carbon bands. Thus butane may be dehydrogenated catalytically to butene and then to butadiene:



The catalyst usually employed is chromic oxide on bauxite, and the operating temperature range is from 450 to 650° C. at atmospheric pressure.

Catalytic *polymerization* is another process for the production of aviation gasoline or high-octane blending agents. Polymerization is a general type of reaction in organic chemistry and may be defined as the combination of two or more molecules of an unsaturated compound to form a larger molecule. Thus isobutene at 350-600 p.s.i. and 175-275° C. in the presence of phosphoric acid yields isoöctene:



$$2\ HC—C{=}CH \xrightarrow{\text{catalyst}} HC—C—CH_2—C{=}CH$$

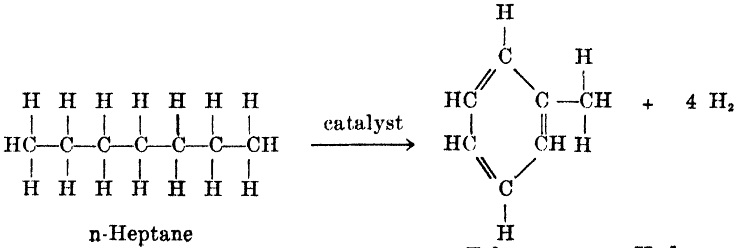
Isobutene

2,2,4 Trimethyl pentene-4
(isoöctene)

The isoöctene is then hydrogenated to isoöctane, using an activated nickel catalyst.

In addition to the branched chain hydrocarbons, petroleum chemists had observed that another class of hydrocarbons also possessed high antiknock properties. These compounds contained their carbon atoms in closed cycles or rings and there were double bonds between alternate carbon atoms. Compounds of this class are known as aromatic hydrocarbons. They will be studied in detail later (see page 407).

The process of converting paraffin hydrocarbons into aromatic hydrocarbons is known as *aromatization* or hydroforming. For example, heptane may be aromatized to toluene:



n-Heptane

Toluene

Hydrogen

The reaction temperatures are about 550° C. and the catalyst is composed of chromic and molybdic oxides.

Without this process for producing toluene needed for the manufacture of TNT (trinitrotoluene), an Allied victory would have been very much more difficult to achieve.

Thus the molecular architects of the petroleum industry, by the use of catalysts and by carefully controlling temperatures and pressures, have been able to perform seeming miracles, and the end is not in sight. It appears that petroleum offers the greatest promise as a source of organic compounds of the future of any raw material.

The question may arise in the minds of some as to why 100-octane gasoline is so important. The answer to this question, in the case of aviation fuel, is that compared to even 91-octane gasoline, 100-octane fuel develops 25 per cent more power at the take-off, maintains the maximum speed of planes at about 1,500 feet higher altitude and saves 100 gallons of fuel on a 600 mile trip.

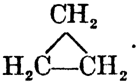
Because of the availability of high octane gasoline, the recent tendency in the design of automobile engines is to utilize continually a higher compression ratio. This is the ratio of the volume of the uncompressed gas in the cylinder to the volume after compression at the top of the piston stroke just before the gaseous mixture is exploded by a spark across the poles of the spark plug.

High compression engines, however, are likely to knock badly, because the compressed gas detonates or explodes suddenly, giving a quick thrust to the piston that results in "knocking." This sudden explosion can be overcome to a certain extent by substituting highly branched hydrocarbons for the normal hydrocarbons; by the addition of certain compounds, such as benzene, to give the so-called benzol blends; or by adding tetraethyl lead ($Pb(C_2H_5)_4$). Most regular gasoline now contains a certain amount of tetraethyl lead; those that contain a high percentage are termed ethyl gasoline.

Because of its lead content, lead-containing gasoline is very toxic. If gasoline is to be used for dry cleaning in the home, a special lead-free gasoline, known as cleaners' naphtha, should be used. It is advisable to use the naphtha in the open air; in a closed room it can constitute a dangerous fire hazard by forming an explosive mixture with air.

Recently the research laboratory of a large automobile manufacturer built an engine with a compression ratio of 12.5 to 1 instead of the 6.5 to 1 ratio used in present engines. The high compression engine installed in a 1946 model car and driven under widely varying conditions gave a 33 per cent better economy in miles per gallon. In city traffic the economy was reported to be over 40 per cent. The gasoline used had an octane number of 88. With a plentiful supply of high octane fuel available we can expect our car of the future to go farther at higher speed on less gasoline.

Cycloparaffins or Naphthenes.—In certain oils from Persia and Russia, and to a lesser extent, those from Texas and California, hydrocarbons known as cycloparaffins or *naphthenes* are present. These compounds are similar to those of the methane series in their properties, except that the carbon atoms are united in a closed cycle, from which the name is derived. The chemical properties are essentially the same as those of the methane or open-chain series; that is, they are characterized by nonreactivity.

The simplest member of the cycloparaffin homologous series is cyclopropane, . Although this hydrocarbon has not been isolated from petroleum, it is of particular interest because of its use in recent years as a general anesthetic. It has been claimed that cyclopropane in some respects is superior to other anesthetics, for with cyclopropane muscular relaxation usually is good, induction and recovery times are short, and there is little postoperative vomiting.

The outstanding disadvantage of cyclopropane, and indeed of all commonly used general anesthetics except chloroform, is the danger of explosion. This fact has been brought to the attention of the surgical world by the occurrence of several fatal explosions in excellent clinics. The usual anesthetic mixture contains about 15 per cent cyclopropane and 85 per cent oxygen, which is well within the explosive range. Since a spark of static electricity may serve to ignite the mixture, attendants at operations where cyclopropane is used as an anesthetic often are requested not to wear silk garments or rubber-soled shoes, which may generate static electricity by friction.

Some of the cycloparaffins that have been identified in petroleum are: cyclobutane, cyclopentane, methylcyclopentane, cyclohexane, methylcyclohexane, 3-dimethylcyclohexane, trimethylcyclohexane, cycloheptane, and cyclooöctane. These products are of special significance in gasoline because of their high antiknock properties.

Recent Developments in Uses of Cracked Gases.—A casual perusal of the recent chemical literature will convince even the neophyte that petroleum, through the medium of the catalytic conversion process, is destined to become the most strategic material of our American industries. By a number of processes, some of which are as yet industrial secrets, the gases obtained from petroleum are being used to produce a wide variety of materials. Some of these are:

1. Ethyl alcohol, otherwise known as grain alcohol.
2. Ethylene glycol, sold as "Prestone." This substance is used as an antifreeze agent for automobile radiators.
3. Benzene. This aromatic hydrocarbon is the starting material for the synthesis of many drugs and dyes as well as phenol which is one component of the Bakelite type of plastics.
4. Styrene. Butadiene and styrene are polymerized to form Buna S, the most widely used of the synthetic rubbers. Styrene is also used for the manufacture of a valuable type of plastic.
5. Glycerol. Formerly this product was obtained mainly as a by-product of the soap industry; now it is potentially available in large quantities from the gases of the cracking process. It is important in the manufacture of explosives, especially dynamite.

6. Butadiene, a product used in the manufacture of Buna, one of the synthetic rubbers.
7. Phthalic anhydride. This compound is in great demand for the manufacture of surface coatings for automobiles, refrigerators, etc.

Other Sources of Petroleum Products.—In addition to the crude oil that occurs in underground pools, oil shale is a potential source of 300 billion barrels of petroleum.

In Europe, where the supply of petroleum is limited, a special process was developed for the hydrogenation of low-grade coal or lignite to give products from which gasoline and lubricating oils can be obtained. The hydrogenation of coal cannot, under normal conditions, compete with petroleum as a source of gasoline and lubricating oils, but with the aid of government subsidies and the need for national self-sufficiency, the process was used in European countries.

Study Questions

1. What was the early distinction between inorganic and organic chemistry? How was this distinction disproved?
2. Define organic chemistry. What are three reasons why it is justifiable to consider the compounds of carbon in a separate class?
3. What are the three most important factors in recall? How can these be utilized in the study of organic chemistry?
4. What is the valence of carbon? From a consideration of the structure of the carbon atom, why is this true?
5. Discuss the tetrahedral concept of the carbon atom.
6. Write the general formula for the paraffin series of hydrocarbons. Name the first ten members of the series.
7. What are four naturally occurring sources of methane?
8. What is the significance of the term *paraffin series* for the series of saturated aliphatic hydrocarbons?
9. What would be the end products of combustion of gasoline if an automobile engine could utilize the available energy 100 per cent?
10. What is the significance of the term *alkyl radical?* Write the names of these radicals for the first ten members of the methane series.
11. Write the equation for the preparation of propane by the Wurtz synthesis.
12. What are the formulas for the possible isomeric pentanes? What type of isomerism do these formulas exemplify?
13. Write graphic formulas for the following hydrocarbons:

(a) 2,2′,3-trimethyl butane (Triptone)
(b) 2,3-Dimethylpentane
(c) 2-Ethyl-3,3′-dimethyldecane

14. What are some of the theories regarding the origin of petroleum?
15. What commercial products can be separated from petroleum by fractional distillation?
16. What is meant by the terms *asphalt base* and *paraffin base* petroleum?
17. What are the principles involved in the cracking process? Why is the process of such great industrial importance?
18. A motor fuel is said to have an octane number of 82. What is the significance of this statement? Could gasoline ever possess an octane number greater than 100?
19. Why is it dangerous to use high test gasoline in the home for dry cleaning purposes?
20. Both propane and cyclopropane contain three carbon atoms, but the latter contains two less hydrogen atoms than the former, yet both are saturated hydrocarbons. How do you account for this seeming contradiction?

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CHAPTER IV

HALOGEN DERIVATIVES OF SATURATED ALIPHATIC HYDROCARBONS

Introduction.—Although paraffin hydrocarbons are characterized by nonreactivity, at high temperatures and in the presence of sunlight or ultraviolet light they will react directly with the halogens, fluorine, bromine, and chlorine, to form compounds in which one or more of the hydrogen atoms in the hydrocarbon molecule are replaced by the halogen. For example, methane will form compounds in which one, two, or even all of the hydrogen atoms are replaced by halogen atoms.

$$
\begin{array}{llll}
1. & CH_4 + Cl_2 & \xrightarrow[\text{sunlight}]{\Delta^*} & CH_3Cl + HCl \\
2. & CH_3Cl + Cl_2 & \longrightarrow & CH_2Cl_2 + HCl \\
3. & CH_2Cl_2 + Cl_2 & \longrightarrow & CHCl_3 + HCl \\
4. & CHCl_3 + Cl_2 & \longrightarrow & CCl_4 + HCl
\end{array}
$$

Iodine, the fourth halogen, does not react when brought in contact with the paraffin hydrocarbons. Indirect methods must be used to prepare the iodine derivatives of the hydrocarbons.

The halogen derivatives of paraffin hydrocarbons do not occur in nature, but, since they are widely used for the preparation of other important compounds, they will be considered here in some detail. The first class of halogen compounds to be discussed is the alkyl halides.

Alkyl Halides.—Alkyl halides can be defined as *monohalogen* derivatives of the paraffin hydrocarbons. The term should not be used loosely, since alkyl halides refer only to those compounds in which *one* hydrogen of the hydrocarbon has been substituted by a halogen. These monohalogen derivatives have the type formula, RX, in which R represents an alkyl radical, and X, one of the halogens.

Alkyl halides usually are not prepared by the direct reaction of a hydrocarbon and the gaseous halogen because, as the foregoing equations illustrate, a mixture of halogenated products results. The separation of any particular compound in pure form is extremely difficult. For this reason, a reaction that gives only one halogenated compound is used.

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*The Greek symbol for delta, Δ, is used to represent heat.

Methyl Chloride, CH_3Cl.—Methyl chloride, also known as monochloromethane, can be prepared by the reaction of phosphorus trichloride or phosphorus pentachloride with methyl alcohol.

$$\underset{\substack{\text{Methyl}\\\text{alcohol}}}{3\ CH_3OH} + \underset{\substack{\text{Phosphorus}\\\text{trichloride}}}{PCl_3} \rightarrow \underset{\substack{\text{Methyl}\\\text{chloride}}}{3\ CH_3Cl} + \underset{\substack{\text{Phosphorous}\\\text{acid}}}{H_3PO_3}$$

or

$$\underset{\substack{\text{Methyl}\\\text{alcohol}}}{CH_3OH} + \underset{\substack{\text{Phosphorus}\\\text{pentachloride}}}{PCl_5} \rightarrow \underset{\substack{\text{Methyl}\\\text{chloride}}}{CH_3Cl} + \underset{\substack{\text{Phosphorus}\\\text{oxychloride}}}{POCl_3} + HCl$$

Commercially, however, methyl chloride usually is prepared by passing hydrogen chloride gas into boiling methyl alcohol in the presence of anhydrous zinc chloride.

$$CH_3OH + HCl \underset{ZnCl_2}{\overset{\text{anhydrous}}{\rightleftarrows}} CH_3Cl + H_2O$$

This reaction is reversible. The use of the catalyst anhydrous zinc chloride catalyst is necessary to secure a substantial yield.

Since the physical and chemical properties of methyl chloride are so similar to those of the other alkyl halides, we shall change our usual procedure of considering the physical and chemical properties of a compound immediately following its mode of preparation, and instead discuss these properties later for the group as a whole (see page 101).

Uses of methyl chloride. Methyl chloride is used widely as a refrigerant in household refrigerators. It is the gaseous substance in the closed refrigerator unit, which is compressed to a liquid by the motor-driven compressor. The liquid then evaporates in the closed jacket surrounding the interior of the refrigerator, taking up heat and cooling the space in which foods are kept.

Methyl chloride is compressed to a liquid and sold in small steel or glass cylinders for use as a local anesthetic for minor operations. This use arises from the fact that its rapid evaporation cools a local area of the body sufficiently to eliminate temporarily the sensation of pain.

Since the boiling point of methyl chloride is 23.7° C., at ordinary temperatures high pressures develop in the steel cylinders containing it. This property, as well as the fact that it is a good solvent for many organic compounds, explains why methyl chloride is widely used as an insecticide propellent in the familiar small aerosol bomb-type sprayers.

Methyl chloride also is used as a methylating agent, a term applied to substances used for the introduction of methyl (CH_3–) groups into organic compounds. In the laboratory synthesis of naturally occurring substances, it is often necessary to introduce at some stage a methyl group in order to give the synthetic compound the same properties as those possessed by the one found in nature.

The large quantity of methyl chloride required for its many uses in industry and in the laboratory is indicated by the fact that in 1946 the production of this alkyl halide was 28,498,000 pounds.

Methyl Bromide, CH_3Br.—Methyl bromide, like methyl chloride, is usually prepared from methyl alcohol rather than from the hydrocarbon. The reaction is brought about by the action of phosphorus tribromide on methyl alcohol.

$$\underset{\substack{\text{Methyl}\\ \text{alcohol}}}{3\ CH_3OH} + \underset{\substack{\text{Phosphorus}\\ \text{tribromide}}}{PBr_3} \rightarrow \underset{\substack{\text{Methyl}\\ \text{bromide}}}{3\ CH_3Br} + \underset{\substack{\text{Phosphorous}\\ \text{acid}}}{H_3PO_3}$$

Another commonly used method of preparation is from methyl alcohol and hydrobromic acid.

$$\underset{\substack{\text{Methyl}\\ \text{alcohol}}}{CH_3OH} + \underset{\substack{\text{Hydrobromic}\\ \text{acid}}}{HBr} \rightarrow \underset{\substack{\text{Methyl}\\ \text{bromide}}}{CH_3Br} + H_2O$$

Methyl bromide (boiling point, 5° C.) is now the most widely used gas for the closed chamber fumigation of a variety of foods. It is well suited to this purpose because of its remarkably low absorption by foods and its high penetration ability.

It has the added advantages of having a vapor density nearly three and a half times that of air and of not being a fire hazard. Methyl bromide is the only compound that has been used successfully for the fumigation of flour under atmospheric pressure in closed chambers. Any infestation of weevil or flour beetles is destroyed by such treatment.

When methyl bromide is being used as a fumigant, proper precautions should be taken, since it is toxic to human beings. It is practically odorless and so gives no warning of its presence. High concentrations show their effect slowly so that an individual may not realize his danger and yet may succumb two or three days later.

Methyl Iodide, CH_3I.—Iodine does not react directly with methane. Methyl iodide ordinarily is prepared by adding the correct amount of phosphorus to methyl alcohol, followed by the addition of iodine. The phosphorus triiodide formed is an intermediate product of the reaction.

$$\underset{\substack{\text{Methyl}\\\text{alcohol}}}{3\ CH_3OH} + \underset{\substack{\text{Phosphorus}\\\text{triiodide}}}{PI_3} \rightarrow \underset{\substack{\text{Methyl}\\\text{iodide}}}{3\ CH_3I} + \underset{\substack{\text{Phosphorous}\\\text{acid}}}{H_3PO_3}$$

The fact that methyl iodide is a *liquid* at ordinary temperatures, while the other methyl halides are gases, is a reflection of its high molecular weight, which results from the presence of the heavy iodine atom. Because methyl iodide is more reactive than the other methyl halides, it is used for methylation reactions and for the preparation of Grignard reagents.

Ethyl Chloride, C_2H_5Cl.—The next higher homologues of the methyl halides are the ethyl halides. Ethyl chloride is manufactured commercially in very large quantities, which probably accounts for the existence of several methods for its preparation. One method is by the action of dry hydrogen chloride gas on ethyl alcohol in the presence of zinc chloride. Another method of manufacture is by the addition of hydrogen chloride to ethylene, an unsaturated hydrocarbon (see page 117).

The major portion of the ethyl chloride produced is consumed in the manufacture of tetraethyl lead. The commercial process consists of the reaction of ethyl chloride with a sodium-lead alloy in an autoclave at moderate temperatures and pressures.

$4\ C_2H_5Cl$	+	$4\ NaPb$	→	$(C_2H_5)_4Pb$	+	$4\ NaCl$	+	$3\ Pb$
Ethyl chloride		Sodium-lead alloy		Tetraethyl lead				

The student will recall that tetraethyl lead is the most widely used compound for improving the antiknock properties of gasoline. The amount of tetraethyl lead added to motor car gasoline ranges from 0.75 ml. to 3.0 ml. per gallon, the legal limit. The more heavily leaded gasolines usually are known to the trade as Ethyl or premium gasolines.

Large quantities of ethyl chloride are consumed in the manufacture of ethyl cellulose, which is used as a plastic, as an ingredient of lacquers, and as a transparent wrapping paper. Ethyl chloride also is employed as a local anesthetic for minor operations, as a refrigerant, and for introducing the ethyl group (C_2H_5—) into organic compounds.

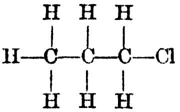
Ethyl Bromide, C_2H_5Br.—Like methyl bromide, ethyl bromide cannot be prepared by the direct action of bromine on the corresponding hydrocarbon. Instead, the compound usually is made by the action of hydrobromic acid on ethyl alcohol. The hydrobromic acid is formed by the action of sulfur dioxide on bromine or by the action of sulfuric acid on sodium bromide.

$NaBr$	+	H_2SO_4	→	HBr	+	$NaHSO_4$
Sodium bromide		Sulfuric acid		Hydrobromic acid		Sodium hydrogen sulfate
HBr	+	C_2H_5OH	→	C_2H_5Br	+	H_2O
Hydrobromic acid		Ethyl alcohol		Ethyl bromide		

Ethyl bromide, a liquid, is used as a local anesthetic, and to a limited extent as an ethylating agent, but its increased reactivity over ethyl chloride does not, in most cases, overbalance its increased cost.

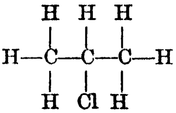
Ethyl Iodide, C_2H_5I.—Ethyl iodide is made by the action of red phosphorus and iodine on ethyl alcohol. At room temperature the reaction is slow, and heating to boiling under a reflux condenser is employed to accelerate the reaction. Because ethyl iodide is the most reactive of the ethyl halides, it is used in laboratory synthesis for the introduction of the ethyl group into compounds, but it is too expensive as yet for most commercial purposes.

Propyl Chloride, C_3H_7Cl. Position Isomerism.—Alkyl halides containing three carbon atoms can be prepared from the corresponding alcohols with the desired configuration of carbon atoms by methods similar to those used for the synthesis of ethyl and methyl chlorides. There are, however, two propyl alcohols; hence, it is possible to obtain two propyl halides. These compounds illustrate the type of isomerism known as *position isomerism.* In this type of isomerism the difference between the isomers is due solely to a difference in the position of one atom or group in the molecule.



$$H-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-Cl$$

n-Propyl chloride
or
1-Chloropropane



$$H-\underset{H}{\overset{H}{C}}-\underset{Cl}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-H$$

Isopropyl chloride
or
2-Chloropropane

The only difference between the two propyl chlorides is the position of the chlorine atom in the molecule. These two compounds have different physical properties even though they have the same molecular formula. Such a phenomenon was defined earlier as isomerism.

Other Alkyl Halides.—Alkyl halides containing more carbon atoms than those already discussed are known, and they can be prepared by the same general methods that have been outlined for the simpler compounds. Some of these compounds are prepared for use as solvents or as reagents for special syntheses.

Alkyl Halides in General.—*Methods of preparation.* There are certain "type" reactions that are applicable to the preparation of the monohalogen derivatives of the hydrocarbons.*

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*Special methods are required for the preparation of the alkyl fluorides.

One method involves the action of a phosphorus-halogen compound on an alcohol. In the following equations, R again is used to represent an alkyl group, and X, a halogen atom.

$3\ ROH$	$+$	PX_3	$\rightarrow$	$3\ RX$	$+$	H_3PO_3
An alcohol		Phosphorus halide		An alkyl halide		Phosphorous acid

Another method of preparation is by the action of a halogen acid on an alcohol in the presence of a catalyst, which in this instance acts also as a dehydrating agent.

$$ROH + HX \rightleftarrows RX + H_2O$$

This latter reaction is best suited for the preparation of the lower halides, that is, those with few carbon atoms in their molecules. The reaction of a halogen acid with alcohol is somewhat analogous to the neutralization of a base by an acid in inorganic chemistry.

$$NaOH + HCl \rightarrow NaCl + H_2O$$

One important difference between these two reactions is that in the neutralization reaction the formation of NaCl is instantaneous, because ions are reacting, while the formation of the alkyl halide is a comparatively slow process since the alcohol is not ionized.

A third method depends on the addition of halogen acid to unsaturated hydrocarbons (see page 121).

Physical properties. As a class the alkyl halides are insoluble in water and soluble in such common organic solvents as alcohol, ether, and acetone. The monohalogen derivatives of the hydrocarbons have a pleasant, sweet odor. They are colorless when pure, although the iodides decompose slowly on standing to become yellow or brown, depending on the amount of free iodine liberated. By reference to Table VII it will be noted that, for a given alkyl group, the boiling point and specific gravity increase in this order: fluorine, chlorine, bromine, and iodine. Methyl fluoride, methyl chloride, methyl bromide, ethyl chloride, and ethyl fluoride are gases at room temperature, but the rest of the lower members of the series are liquids. The first solid alkyl halide is $C_{15}H_{31}I$. In general, for a given halogen compound the boiling point increases with an increase in the molecular weight of the alkyl group.

TABLE VII

PHYSICAL CONSTANTS OF ALKYL HALIDES

COMMON NAME	FORMULA	B.P. °C.	SP. GR. 20°/4°
Methyl iodide	CH_3I	43	2.279
Ethyl iodide	CH_3CH_2I	72	1.933
n-Propyl iodide	$CH_3CH_2CH_2I$	102	1.747
Isopropyl iodide	CH_3CHICH_3	89	1.703
n-Butyl iodide	$CH_3CH_2CH_2CH_2I$	129	1.617
Methyl bromide	CH_3Br	5	1.732
Ethyl bromide	CH_3CH_2Br	38	1.430
n-Propyl bromide	$CH_3CH_2CH_2Br$	71	1.353
Isopropyl bromide	$CH_3CHBrCH_3$	60	1.310
n-Butyl bromide	$CH_3CH_2CH_2CH_2Br$	101	1.275
Methyl chloride	CH_3Cl	-24	0.920
Ethyl chloride	CH_3CH_2Cl	12	0.910
n-Propyl chloride	$CH_3CH_2CH_2Cl$	47	0.890
Isopropyl chloride	$CH_3CHClCH_3$	37	0.860
n-Butyl chloride	$CH_3CH_2CH_2CH_2Cl$	78	0.884
Methyl fluoride	CH_3F	-78	0.877
Methyl chloride	CH_3Cl	-24	0.920
Methyl bromide	CH_3Br	5	1.732
Methyl iodide	CH_3I	43	2.279

Chemical properties. The hydrocarbon residues in the alkyl halides have practically the same reactivity as the original hydrocarbons. Accordingly, the alkyl halides as a group are relatively nonreactive. Because of this relative stability, they are used widely as solvents, one requirement of a good solvent being that it will not react with the dissolved material.

The most important chemical reactions are those that involve the functional group.* One difference between organic and inorganic compounds is that, as a rule, organic compounds in solution are not ionized or are ionized only to a slight extent. For example, in the case of the alkyl chlorides, there is no reaction with an aqueous solution of silver nitrate, whereas the reaction of aqueous silver nitrate with an inorganic chloride, like sodium chloride, results in the immediate formation of silver chloride. In order to bring about reactions between alkyl halides and various other substances, it usually is necessary to heat the materials for a considerable time.

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*The functional group is the reactive atom or group present in a molecule.

In the presence of water the alkyl halides react with hydroxides to form alcohols. This is a very useful laboratory method of preparing the less common alcohols.

$$\underset{\substack{\text{An alkyl}\\ \text{halide}}}{RX} + NaOH \xrightarrow{H_2O} \underset{\text{An alcohol}}{ROH} + NaX$$

The student should remember that this is the course of the reaction only when alkyl halides react with alkalies in the presence of *water*. If the same reaction takes place in an alcoholic solution, an unsaturated hydrocarbon is formed (see page 119).

Alkyl halides react with inorganic cyanides to form nitriles.

$$RX + KCN \rightarrow \underset{\text{A nitrile}}{RCN} + KX$$

The cyanide group in the nitrile then can be made to react with water to form the carboxyl group characteristic of organic acids.

Hydrocarbons are formed by the reaction of an alkyl halide with an active metal, such as sodium (Wurtz reaction, see page 70).

$$2\ RX + 2Na \rightarrow RR + 2\ NaX$$

For example:

$$\underset{\text{Methyl iodide}}{2\ CH_3I} + 2\ Na \rightarrow \underset{\text{Ethane}}{H_3C\text{–}CH_3} + 2\ NaI$$

The student will be aided in writing the various equations involving alkyl halides and in understanding their uses if he bears in mind that the reactivity of the alkyl halides in the order of *increasing* activity is fluorides, chlorides, bromides, and iodides. This is the opposite of the chemical activity of the free halogens, a fact that may afford the student an association that will aid him in recalling this information. Since chlorine is so much more active than iodine, its combination with the alkyl radical is brought about more easily, the reaction is more vigorous, and the product formed is more stable than is the case with iodine. There is less tendency for the molecule to "break up" and react with some other substance. Iodine, on the other hand, is more difficult to bring into combination, and when the compound is formed, it is less firmly held together than is the case for chlorine compounds. Even though the alkyl chlorides are less reactive than the other common alkyl halides, they are more often used industrially because of their low cost. Their unreactivity is overcome to a large extent by operating under pressure and at high temperatures.

Grignard Reagents.—One of the most important tools of the organic chemist is a class of compounds that results from the reaction between alkyl halides and magnesium in the *absence of water.* This reaction was discovered by Grignard, a French chemist, and the reaction has been named in his honor. Reactions that have been named after their discoverer are very numerous in organic chemistry. Probably this is a better way to perpetuate a name for posterity than to have it inscribed on some mausoleum. In recognition of his discovery, Grignard was awarded half of the Nobel Prize for chemistry in 1912.

The following equations illustrate the formation of Grignard reagents from an alkyl halide:

$$\underset{\text{Alkyl halide}}{RX} + Mg \xrightarrow[\text{absence of water}]{\text{ether}} \underset{\text{Grignard reagent}}{RMgX}$$

$$\underset{\substack{\text{Methyl}\\\text{chloride}}}{CH_3Cl} + Mg \xrightarrow[\text{absence of water}]{\text{ether}} \underset{\substack{\text{Methyl magnesium}\\\text{chloride}}}{CH_3MgCl}$$

The reaction flask and all chemicals must be absolutely dry, for if water is present, the Grignard reagent will react with the water to form hydrocarbons, and thus will not be available for other usually more desirable reactions. Grignard reagents, of which methyl magnesium chloride is an example, are among the most widely used reagents in synthetic organic chemistry. The specific reactions in which Grignard reagents are involved will be mentioned later when the compounds formed are discussed.

The Grignard reagents are examples of a class of compounds in which a metallic element is combined directly with a carbon atom. These compounds are termed *organometallic* compounds. Recently there has been an increased use of the organolithium compounds (RLi) because, in general, they are more reactive than the organomagnesium compounds. They are formed by the reaction of metallic lithium with the RMgX compounds.

Although silicon is nonmetallic in its properties, organic compounds of silicon are often included in discussions of organometallic compounds. Since alkyl halides are employed in the preparation of an important group of the organosilicon compounds and because of their many recent industrial applications, we shall consider briefly the chemistry of the silicones.

From the standpoint of practical applications, the most important organosilicon compounds are those of the type, R_2SiO. However, in order to understand the naming and synthesis of these compounds it is necessary first to consider other compounds of silicon. From the standpoint of structure the simplest covalent compound of silicon is the hydride, SiH_4, named *silane*. Because of the relation in structure the compound $(CH_3)_2SiCl_2$ is called dimethyl-dichlorosilane. There are two general methods of preparing these dialkylhalosilanes.

In the *direct method*, alkyl halides in the liquid or vapor phase react with elementary silicon in the presence of a copper catalyst. The reaction with methyl chloride is given as a specific example.

$$\underset{\text{Methyl chloride}}{2\ CH_3Cl} + \underset{\text{Silicon}}{Si} \xrightarrow{Cu} \underset{\text{Dimethyl-dichlorosilane}}{(CH_3)_2SiCl_2}$$

In the *substitution methods*, the Grignard reaction is now used in plant-scale operations.

$$\underset{\text{Methyl chloride}}{CH_3Cl} + \underset{\text{Magnesium}}{Mg} \xrightarrow{\text{Dry ether}} \underset{\text{Methyl magnesium chloride}}{CH_3MgCl}$$

$$2\ CH_3MgCl + \underset{\text{Silicon tetrachloride}}{SiCl_4} \rightarrow (CH_3)_2SiCl_2 + 2\ MgCl_2$$

The dimethyl-dichlorosilane obtained by the use of either of these general methods is then hydrolyzed to the desired dimethylsiloxane.

$$(CH_3)_2SiCl_2 + H_2O \rightarrow \underset{\substack{\text{Dimethylsiloxane} \\ \text{(methyl silicone)}}}{(CH_3)_2SiO} + 2\ HCl$$

Under various conditions and by selected methods, methyl silicone and similar compounds can be caused to add repeatedly to each other to form polymers with unique and useful properties.

The low molecular weight silicone polymers are oils that are remarkable for their small change in viscosity with changes in temperature and their chemical inertness. These properties make them of special value as lubricants and hydraulic fluids. A specific example of the relatively small change of viscosity of a silicone oil may be helpful.

At 100° F. a silicone oil and an ordinary hydrocarbon lubricating oil both had a viscosity index of 100. After cooling both oils to –35° F. it was found that the silicone oil had seven times its former viscosity while the hydrocarbon oil had increased 1800 fold in viscosity.

The silicone resins have a higher molecular size than the silicone oils and greases. Silicone resins used in protective and decorative finishes have shown excellent resistance to heat, weather, and various chemicals. When pigmented with heat-resisting pigments, these finishes withstand 1000° F. for a few hours and 500° F. for several hundred hours. Since silicone finishes are so new and facilities for producing them are limited, they have not been used widely. If volume production reduces cost, the silicone resins appear to have a bright future.

Silicone rubbers, if compared to the silicone oils and resins, are superpolymers of high molecular weight. In common with the other silicone polymers, silicone "rubber" or elastomer shows exceptional thermal stability. This material does not melt when heated in air at 300° C. and its elasticity persists at –55° C. In addition it has excellent electrical insulating properties.

Silicone rubbers are odorless, tasteless, and nontoxic. These properties have made it possible to build wire-cloth reinforced belts for use in the food processing industries. Foods are placed directly on the belts and although the belt temperatures may reach 225° C. during dehydration of the food, the rubber is unaffected and contributes no objectional flavor to the food.

Silicone elastomers are being used to replace rubber in the core of golf balls.

Dihalogen Derivatives of Paraffin Hydrocarbons. Methylene Halides.—The dihalogen derivatives of the methane series are less frequently encountered than the alkyl halides. They are made usually from the higher halogen derivatives, as for example:

$$\underset{\text{Chloroform}}{CHCl_3} + \underset{\substack{\text{Nascent}\\\text{hydrogen}}}{2\,[H]} \xrightarrow[Zn]{HCl} \underset{\substack{\text{Methylene}\\\text{chloride}}}{CH_2Cl_2} + HCl$$

Methylene chloride is used as a refrigerant in air-conditioning equipment and as a solvent in the extraction of caffeine from coffee and tea. Methylene chloride is the liquid in the "Bubble-Lite" type of Christmas tree lights. It is important for the student to remember that the $-CH_2-$ group is known as the *methylene group,* for it will be encountered frequently in organic chemistry.

Methylene iodide, CH_2I_2 (diiodomethane), because of its high percentage of iodine, has the unusual property of having a specific gravity of 3.325, far greater than that of common liquids other than mercury. Liquids with specific gravities from 0.878 to 3.325 can be obtained by mixing methylene iodide and benzene in various proportions. Such liquids are used for the gravity separation of refuse material in the processing of ores. The specific gravity of the liquid is adjusted so that one material sinks while the other floats.

Methylene iodide can be prepared by the action of hydriodic acid on iodoform.

$$\underset{\text{Iodoform}}{HCI_3} + \underset{\substack{\text{Hydriodic}\\\text{acid}}}{HI} \rightarrow I_2 + \underset{\substack{\text{Methylene}\\\text{iodide}}}{CH_2I_2}$$

Dihalogen derivatives of higher homologues of methane generally are made from the unsaturated hydrocarbons, and they will be considered in our discussion of this class of hydrocarbons.

Chloroform, $CHCl_3$.—Chloroform, the compound in which three chlorine atoms have been substituted for three hydrogen atoms of the methane molecule, has the chemical name trichloromethane. It is not prepared directly by the action of chlorine on methane, but is made by the reduction of carbon tetrachloride with moist iron.

$$\underset{\substack{\text{Carbon}\\\text{tetrachloride}}}{CCl_4} + 2\ [H] \xrightarrow[H_2O]{Fe} \underset{\substack{\text{Chloroform}\\\text{or}\\\text{trichloromethane}}}{CHCl_3} + HCl$$

Chloroform is a colorless liquid with a pleasant odor. It is insoluble in water, but is soluble in the organic solvents. It was one of the first substances (1848) to be used as a general anesthetic, and it is still employed for this purpose, although to a limited extent. Chloroform has the advantage over other anesthetics in being noninflammable. It still is used in country practices where open flame lamps must be used.

One important reason that chloroform is not being more widely used is the fact that in rare cases it causes death by poisoning the heart muscles or the liver. Also, it reacts with oxygen in the presence of light to form phosgene, a poison gas used in World War I.

$$\underset{\text{Chloroform}}{2\ CHCl_3} + O_2 \rightarrow \underset{\substack{\text{Phosgene or}\\\text{carbonyl chloride}}}{2\ COCl_2} + 2\ HCl$$

To retard the formation of phosgene, chloroform is kept in brown bottles or in metal cans that are filled as completely as possible to exclude air, and to which about 1 per cent of alcohol has been added.

Chloroform is an excellent solvent for fats, rubber, and other organic compounds.

Bromoform, $CHBr_3$.—Bromoform, the halogen derivative of methane that contains three bromine atoms in each molecule, is a colorless liquid made by treating alcohol with bromine and alkali. It has some uses as a drug.

Iodoform, CHI_3.—When three hydrogen atoms of methane are replaced by iodine atoms, the resulting compound is a lemon-yellow, crystalline solid with a persistent odor. It is known as iodoform. Before the drug department of "drugstores" was relegated to an inconspicuous corner, the characteristic odor that pervaded pharmacies was due mainly to iodoform. Formerly it was used widely as an antiseptic because of its property of slowly decomposing with the liberation of free iodine. Now it is seldom used on account of its pungent odor and because other compounds with superior germicidal properties have replaced it. Iodoform is made by heating alcohol with iodine and alkali.

$$\underset{\text{Ethyl alcohol}}{C_2H_5OH} + 4\,I_2 + 6\,NaOH \rightarrow 5\,NaI + 5\,H_2O + \underset{\text{Sodium formate}}{HCO_2Na} + \underset{\text{Iodoform}}{HCI_3}$$

The formation of iodoform, as illustrated in this reaction, is often used as a positive test for alcohol in an unknown solution.

Carbon Tetrachloride, CCl_4.—The fully substituted chlorine derivative of methane bears the chemical name of tetrachloromethane and is commonly known as carbon tetrachloride. Commercially, it is not made by the direct reaction between chlorine and the hydrocarbon, but rather by passing chlorine into carbon disulfide. Iron, iodine, or antimony pentasulfide is used as a catalyst.

$$\underset{\text{Carbon disulfide}}{CS_2} + 3\,Cl_2 \xrightarrow{I_2} \underset{\text{Carbon tetrachloride}}{CCl_4} + \underset{\text{Sulfur chloride}}{S_2Cl_2}$$

Carbon tetrachloride is a water-clear liquid with a pleasant odor. It is insoluble in water, but soluble in the organic solvents. Because of the high proportion of chlorine in the molecule it is not combustible, and since it volatilizes easily, it is used in the hand type "Pyrene" fire extinguisher. It is effective as a fire extinguisher because it cuts off the supply of oxygen and absorbs 47 calories per gram evaporated, thus often cooling the material below the kindling point. It is very effective for oil fires and fires where there are dangerous electric currents. Breathing the vapors of carbon tetrachloride has a bad effect on the heart and causes severe headaches. In the case of very hot fires, such as ether fires in the laboratory, considerable quantities of phosgene, a poisonous gas, are formed. Good ventilation should always follow the use of carbon tetrachloride as a fire extinguisher.

Carbon tetrachloride is used for the commercial manufacture of chloroform and as a solvent for fats, rubber, and other organic substances. It is often added to solvents, such as naphtha gasoline used in dry cleaning, to reduce the fire hazard that is present when such large quantities of gasoline are used. The commercial product, Carbona, owes its effectiveness in dry cleaning and its noninflammability to the fact that it is mainly carbon tetrachloride. Taken internally in proper doses, carbon tetrachloride is effective in the treatment of hookworm. Large doses are poisonous.

Sink-Float Process.—Pentachloroethane and tetrabromoethane are used in the ''sink-float'' process for the gravity separation of coal from refuse materials. Mixtures of these halogen hydrocarbons can be prepared so as to have a high enough specific gravity to float coal, whereas rock, slate, and other noncombustible materials sink to the bottom. In carrying out the process, the mixture of coal and slate is treated with an ''active agent'' to prevent the adherence of the active liquids to the coal. The discovery that picric acid could serve this purpose made the process practicable commercially. When picric acid is used, only about one-half pint of the chlorinated hydrocarbons are lost per ton of the processed coal and slate.

The sink-float process is not restricted to the mining of coal; it can be applied to the processing of lead, copper, and other ores. The development of the gravity-separation process makes available huge supplies of low-grade ores that could not be mined profitably by earlier methods.

Fluorine Compounds.—Urgent wartime requirements greatly accelerated research on the chemistry of organic fluorine compounds, and the development of means of preparing them. It appears that this development may have opened up a whole new field of organic chemistry. For a detailed discussion the original papers should be consulted. Reference to a recent symposium on fluorine chemistry is given at the end of this chapter.

The preparation of fluorine compounds by the direct reaction between hydrocarbons and fluorine requires special conditions since such reactions often take place with explosive violence. A more generally used method involves the chlorination of a suitable starting material and replacement of most of the chlorine with fluorine by the use of anhydrous hydrogen fluoride in the presence of antimony salts. Further fluorination is obtained by the use of silver difluoride (AgF_2) or cobalt trifluoride (CoF_3). The preparation of chloroperfluoroheptane by this method is illustrated by the following equations.

$$C_7H_{16} + 12\ Cl_2 \xrightarrow[\text{light}]{\text{ultraviolet}} C_7H_4Cl_{12} + 12\ HCl$$

$$C_7H_4Cl_{12} + 10\ HF \xrightarrow{SbCl_5} C_7H_4Cl_2F_{10} + 10\ HCl$$

$$C_7H_4Cl_2 + 9\ AgF \longrightarrow \underset{\substack{\text{Chloroperfluoro-}\\ \text{heptane}}}{C_7ClF_{15}} + Cl_2 + 4\ HF + 9\ AgF$$

By carefully controlling the conditions, fluorocarbons can be prepared by the fluorination of hydrocarbons with cobalt trifluoride. The equation for the fluorination of n-heptane is:

$$C_7H_{16} + 32\ CoF_3 \rightarrow C_7F_{16} + 32\ CoF_2 + 16\ HF$$

The cobalt difluoride formed during the reaction is reconverted to the trifluoride with fluorine gas.

$$2\ CoF_2 \quad + \quad F_2 \quad \rightarrow \quad 2\ CoF_3$$

Interest in fluorocarbons was aroused in 1941 when it appeared that their availability would greatly facilitate the separation of uranium isotopes for use in the production of atomic bombs. The fluorocarbons are characterized by extreme thermal stability and resistance to chemical action so that they should find many valuable peacetime uses in industry. Research work completed and in progress makes it probable that some uses of the fluorocarbons will be as heat transfer and dielectric media, fire extinguishers, turbine impellants, high temperature lubricants, and noninflammable, nontoxic anesthetics.

It is important to remember that the unusual stability of the polyfluorides is exhibited only when at least two fluorine atoms are attached to one carbon. The compounds in which only one fluorine atom is attached to a carbon atom are generally so reactive as to be unstable.

A compound that was manufactured in quantity before World War II is *dichlorodifluoromethane* (Freon 12). It is prepared by the action of anhydrous hydrogen fluoride on carbon tetrachloride in the presence of antimony salts.

$$\underset{\substack{\text{Carbon}\\ \text{tetrachloride}}}{CCl_4} + \underset{\substack{\text{Hydrogen}\\ \text{fluoride}}}{2\ HF} \xrightarrow{SbCl_5} \underset{\substack{\text{Dichlorodi-}\\ \text{fluoromethane}}}{CCl_2F_2} + 2\ HCl$$

Dichlorodifluoromethane is ideally suited for its wide use in household refrigerators and air conditioning units because it is nontoxic, noninflammable, and does not corrode moist metals. The physiological inertness of CCl_2F_2 has been illustrated by keeping animals for weeks in an artificial atmosphere of 20 per cent O_2, 40 per cent N_2, and 40 per cent CCl_2F_2 without any ill effects. The properties of CCl_2F_2 make it particularly valuable for use as the refrigerant in air conditioning units for public places such as theaters as many deaths might result from leaking refrigerant if it were toxic, and panics might result if it had a pungent odor.

Polytetrafluoroethylene (Teflon) is a new plastic with a stability unique among organic compounds. No substance has been found that will dissolve or even swell this plastic. It is not attacked below 300° C. by any corrosive agent except molten alkali metals. It can be heated at 300° C. for several hours with no appreciable loss in weight and even at –100° C. films of this material are flexible. In addition to these remarkable properties, polytetrafluoroethylene has been found to have excellent electrical insulating properties. Some current uses of this plastic are for electrical insulation and as gaskets and packing in equipment for handling hot corrosive liquids.

Study Questions

1. Define alkyl halides. What is their type formula?
2. Why are alkyl halides not prepared usually by the direct reaction of a halogen and a saturated hydrocarbon?
3. What properties of methyl chloride make it valuable as a refrigerant?
4. What is a methylating agent? What class of alkyl halides is used most successfully for methylation reactions and why?
5. What is an important industrial use of ethyl chloride?
6. How does position isomerism differ from chain isomerism?
7. Write a general equation for the preparation of alkyl halides.
8. What is the functional group in isopropyl chloride?
9. Write an equation for the formation of nonyl alcohol involving the use of an alkyl halide.
10. Write an equation for the preparation of butane using ethyl bromide as a starting material. This is an example of what "name reaction"?
11. What class of alkyl halides are the most reactive? Why are they not as widely used as the alkyl chlorides?
12. What is the type formula for a Grignard reagent? How can it be prepared?
13. What is the common name for the compound formed when three atoms of hydrogen of methane are substituted for three atoms of chlorine? Give several uses for this compound.
14. What is the common name for tetrachloromethane? What are two uses of this compound?
15. Describe the principles involved in the "sink-float" process used in ore mining. What halogen derivatives are used in the process?
16. Why is chloroform not used much as a general anesthetic?
17. One test for the presence of an alcohol in an unknown solution is to heat it with iodine and alkali. What constitutes a positive result and how can it be recognized?
18. What is Freon-12 and for what is it used? What properties make it well suited to this use?
19. Explain why the reactivity of the chlorine atom in CH_3Cl is so much less than its reactivity in $NaCl$.

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CHAPTER V

UNSATURATED ALIPHATIC HYDROCARBONS

Introduction.—In Chapter III we discussed compounds, termed saturated or paraffin hydrocarbons, composed of carbon and hydrogen. We now come to another group of compounds, consisting of only carbon and hydrogen, but containing less hydrogen per carbon atom than those of the paraffin series. For example, a chemical compound that is a gas and is composed of only carbon and hydrogen is analyzed and found to have the molecular formula C_2H_4. This compound has been named ethylene; it is the first member of an homologous series known as the *olefin, alkene,* or *ethylene* series. The type formula of the series is C_nH_{2n}. These compounds are referred to as *unsaturated* hydrocarbons in contrast to the *saturated* or paraffin hydrocarbons. The members of the ethylene series combine with halogens, such as bromine and chlorine, by direct addition instead of by substitution of hydrogen atoms, as is true in the case of the methane series. In other words, all four valences of carbon in unsaturated compounds are not satisfied by hydrogen or by other elements or groups. Early organic chemists observed that when chlorine reacted with these unsaturated hydrocarbons, the products were oily liquids. Because of this property, the name olefin, meaning oily, was given to the whole series.

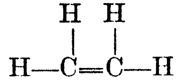
Olefin Series.—The simplest unsaturated hydrocarbons contain two less hydrogen atoms per molecule than do the corresponding members of the paraffin series. In naming these

TABLE VIII

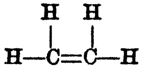
PHYSICAL CONSTANTS OF SOME UNSATURATED HYDROCARBONS

MOLECULAR FORMULA	COMMON NAME	I.U.C. NAME	M.P. ° C.	B.P. ° C.
C_2H_4	Ethylene	Ethene	-169.4	-103.8
C_3H_6	Propylene	Propene	-185.2	- 47.0
C_4H_8	n-Butylene	1-Butene	-130.0	- 6.7
C_5H_{10}	n-Amylene	1-Pentene	-138.0	40.0
C_6H_{12}	n-Hexylene	1-Hexene	- 98.5	64.1

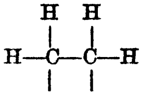
compounds, according to the International Union of Chemistry system, the *ane* ending of the paraffin series is changed to *ene;* however, the more commonly used ending is *ylene.* Table VIII shows some of the physical constants of members of the olefin series.

Ethylene.—The simplest compound of the olefin series is ethylene, represented by the graphic formula  $H-\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}-H$. The evidence and the reasoning that lead to this graphic formula can be better appreciated and understood by the student if he will imagine himself in a laboratory confronted with the problem of determining the correct graphic formula for ethylene.

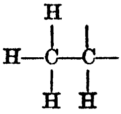
Assuming that the pure gaseous hydrocarbon has been isolated with the materials available in any well-equipped laboratory, it will be possible to analyze the compound for the percentage content of carbon and hydrogen. This will show that there are two atomic weights of hydrogen for each atomic weight of carbon. A molecular weight determination will demonstrate that the molecular formula of ethylene is C_2H_4. Keeping in mind the fundamental concept that in most organic compounds carbon has a valence of 4, there are three possibilities for representation of the graphic formula of the compound.


$H-\overset{H}{\overset{|}{C}}=\overset{H}{\overset{|}{C}}-H$

A


$H-\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{H}{\overset{|}{C}}}-H$

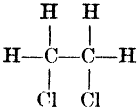
B


$H-\underset{\underset{H}{|}}{\overset{H}{\overset{|}{C}}}-\underset{\underset{H}{|}}{\overset{|}{C}}-$

C

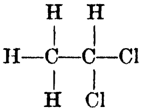
Valences on adjoining carbon atoms do not remain unsatisfied for more than a very small fraction of a second; consequently, the unsaturated valence on each carbon atom in B will unite with the other to form what is known as a double bond, as is represented in formula A. A and C are then the two remaining possibilities.

Experiments show that ethylene will combine with chlorine to give a compound that by quantitative analysis can be demonstrated to have the molecular formula $C_2H_4Cl_2$. There are two compounds actually known that have this formula, but each has different chemical and physical properties. It follows that the structural arrangement of the atoms in the two compounds must be different. Two possible patterns or configurations of the atoms can be obtained by adding chlorine to formulas *A* and *C*.



$$\begin{array}{ccccc} & H & & H & \\ & | & & | & \\ H- & C & - & C & -H \\ & | & & | & \\ & Cl & & Cl & \end{array}$$

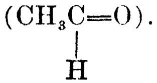
Results from formula
A



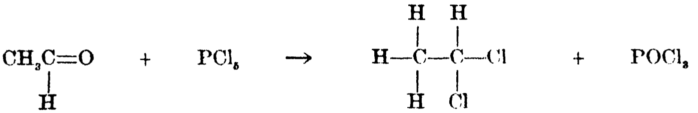
$$\begin{array}{ccccc} & H & & H & \\ & | & & | & \\ H- & C & - & C & -Cl \\ & | & & | & \\ & H & & Cl & \end{array}$$

Results from formula
C

In order to prove which one of these compounds results from the reaction of chlorine and ethylene, it is necessary to present a reaction, the correctness of which the student must take on faith at this point, but which will be considered later. This reaction is that of phosphorus pentachloride (PCl_5) with acetaldehyde



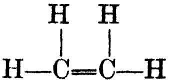
$$(\begin{array}{c} CH_3C{=}O \\ \;\;| \\ \;\;H \end{array}).$$



$$\begin{array}{c} CH_3C{=}O \\ \;\;| \\ \;\;H \end{array} + PCl_5 \rightarrow \begin{array}{ccccc} & H & & H & \\ & | & & | & \\ H- & C & - & C & -Cl \\ & | & & | & \\ & H & & Cl & \end{array} + POCl_3$$

Acetaldehyde — Phosphorus pentachloride — Ethylidene chloride (B.P. 57.3° C.)

It has been demonstrated by a number of careful experiments that, in the foregoing type of reaction with phosphorus pentachloride, chlorine atoms take the place of the oxygen atom in acetaldehyde. The compound that is obtained from acetaldehyde carries 2 chlorine atoms on *one* carbon atom and has a boiling point of 57.3° C. On the other hand, the compound that actually is obtained by the reaction of ethylene and chlorine has a boiling point of 83.7° C. Accordingly, the compound from the reaction of ethylene and chlorine cannot have 2 chlorine atoms on one carbon atom, but must have, instead, one chlorine atom on each carbon atom. This is possible only if formula *A*, namely,



$$\begin{array}{ccccc} & H & & H & \\ & | & & | & \\ H- & C & = & C & -H \end{array}$$

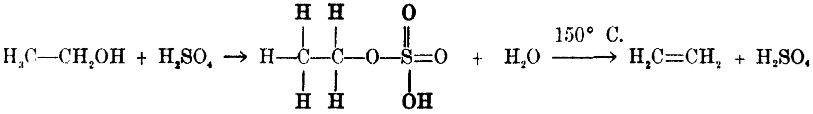
, represents the true graphic formula for ethylene.

Preparation. Ethylene can be prepared commercially by the dehydration of ethyl alcohol with the use of heat and a catalyst.

$$\underset{\text{Ethyl alcohol}}{H_3C{-}CH_2OH} \xrightarrow[300°\text{-}400°\ C.]{Al_2O_3} \underset{\text{Ethylene}}{H_2C{=}CH_2} + H_2O$$

Large quantities of ethylene are produced by cracking propane obtained from natural gas, and also by cracking gas oil and other petroleum fractions.

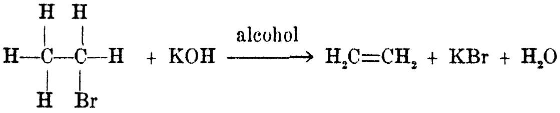
A laboratory method for the preparation of ethylene is the dehydration of ethyl alcohol by means of sulfuric acid or phosphoric acid.



$$H_3C{-}CH_2OH + H_2SO_4 \rightarrow H{-}\underset{H}{\overset{H}{C}}{-}\underset{H}{\overset{H}{C}}{-}O{-}\underset{OH}{\overset{O}{\overset{\|}{S}}}{=}O + H_2O \xrightarrow{150°\ C.} H_2C{=}CH_2 + H_2SO_4$$

Ethyl alcohol | Ethyl hydrogen sulfate | **Ethylene**

In addition, ethylene can be prepared by heating an ethyl halide with alcoholic potassium hydroxide.

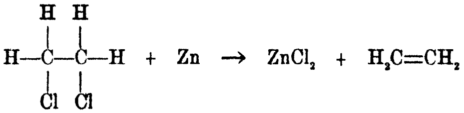


$$H{-}\underset{H}{\overset{H}{C}}{-}\underset{Br}{\overset{H}{C}}{-}H + KOH \xrightarrow{\text{alcohol}} H_2C{=}CH_2 + KBr + H_2O$$

Ethyl bromide | Ethylene

The presence of alcohol in the reaction mixture is an important point to bear in mind, for it was seen (page 104) that alkyl halides in an *aqueous* alkaline medium yield alcohols.

Ethylene can be prepared by distilling a dihalogen compound with zinc.



$$H{-}\underset{Cl}{\overset{H}{C}}{-}\underset{Cl}{\overset{H}{C}}{-}H + Zn \rightarrow ZnCl_2 + H_2C{=}CH_2$$

Ethylene dichloride* | Ethylene

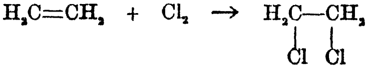
Properties. Ethylene is a colorless gas with a pleasant, sweetish odor. It is only slightly soluble in water, but dissolves read-

---

*By common usage this compound is called *ethylene* dichloride (commercially it is prepared from ethylene) instead of the I.U.C. name, 1, 2-dichloroethane.

ily in acetone and other organic solvents. It burns with a luminous, smoky flame, and mixtures of from 3 to 29 per cent with air are explosive.

The student will note that two straight lines are used to represent a "double bond" in ethylene. This is a means of representing the fact that two valences, or combining powers, of the carbon atom are mutually satisfied. The student should be warned against concluding that the words, double bond, and the graphic manner of representing it, mean that the carbon atoms are held together twice as firmly as in the case of a single bond. The combining power represented by a single bond is sufficient for a stable union of the carbon atoms; hence, when carbon atoms are joined by two bonds, not all of the combining power of either bond is required, so that there remains a residual affinity available for combining with other elements or radicals. It follows, therefore, that the most important chemical reaction of ethylene is the "opening-up" of the double bond to add two monovalent elements or groups. Accordingly, a typical reaction of ethylene is the addition of halogens.



$$H_2C{=}CH_2 + Cl_2 \rightarrow \underset{Cl}{\underset{|}{H_2C}}{-}\underset{Cl}{\underset{|}{CH_2}}$$

Ethylene — Ethylene chloride or ethylene dichloride

Chlorosol, a mixture of ethylene chloride and carbon tetrachloride in the ratio of 3:1 by volume, is used as a liquid fumigant for insect pests in mills and grain elevators.

Large quantities of ethylene chloride are used in the manufacture of Thiokol, one of the synthetic rubbers. Ethylene chloride also is used as a solvent for fats, waxes, and greases, and as a minor component in "Ethyl Fluid" for addition to gasoline.

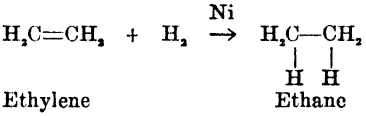
If ethylene chloride is treated with chlorine at 400° C., 1,1,2,2-tetrachloroethylene (perchloroethylene) is formed.

$$\underset{\text{Ethylene dichloride}}{ClCH_2CH_2Cl} + 3\ Cl_2 \xrightarrow{400^\circ} \underset{\text{Perchloroethylene}}{Cl_2C{=}CCl_2} + 4\ HCl$$

Perchloroethylene, sold under the trade name Perclene, is used extensively as a dry cleaning agent. It is noninflammable, does not corrode metals, and has a lower toxicity than most other chlorinated solvents.

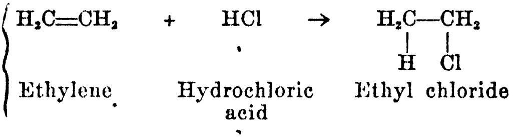
Ethylene bromide ($BrCH_2CH_2Br$) is prepared by the direct addition of bromine to ethylene. Large quantities are used with tetraethyl lead in "Ethyl Fluid." The function of ethylene bromide and ethylene chloride is to prevent deposition of lead oxide in the cylinders. This is accomplished by the formation of volatile lead bromide and lead chloride, which are swept out of the cylinder in the exhaust gases.

When finely divided nickel is used as a catalyst, ethylene unites with hydrogen to form a saturated compound.



$$\underset{\text{Ethylene}}{H_2C{=}CH_2} + H_2 \xrightarrow{Ni} \underset{\text{Ethane}}{\underset{H}{H_2C}\!-\!\underset{H}{CH_2}}$$

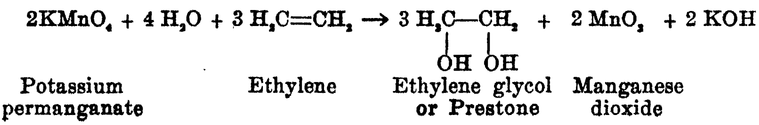
The halogen acids add directly to ethylene to give alkyl halides.



$$\underset{\text{Ethylene}}{H_2C{=}CH_2} + \underset{\text{Hydrochloric acid}}{HCl} \rightarrow \underset{\text{Ethyl chloride}}{\underset{H}{H_2C}\!-\!\underset{Cl}{CH_2}}$$

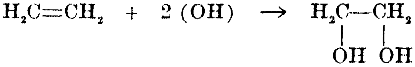
Most of the large quantity of ethyl chloride needed in the manufacture of tetraethyl lead is made in this way.

Another reaction of ethylene is known as *Baeyer's test for unsaturation.* The student will recall the deep purple color that a small amount of potassium permanganate ($KMnO_4$) imparts to an aqueous solution. If ethylene is bubbled into a slightly alkaline solution of potassium permanganate, the color disappears, and a brown precipitate of manganese dioxide appears. This reaction was discovered by Adolf von Baeyer, and is a very important one, because it is used in testing for the presence of double bonds in organic compounds.



$$\underset{\text{Potassium permanganate}}{2KMnO_4} + 4\,H_2O + \underset{\text{Ethylene}}{3\,H_2C{=}CH_2} \rightarrow \underset{\text{Ethylene glycol or Prestone}}{3\,\underset{OH}{H_2C}\!-\!\underset{OH}{CH_2}} + \underset{\text{Manganese dioxide}}{2\,MnO_2} + 2\,KOH$$

The foregoing reaction is essentially the addition of two hydroxyl groups to ethylene (or to any compound at the point of the double bond). If the compounds that contribute these radicals are omitted, the basic reaction can be expressed as:



$$H_2C{=}CH_2 + 2\,(OH) \rightarrow \underset{OH}{\underset{|}{H_2C}}{-}\underset{OH}{\underset{|}{CH_2}}$$

Uses. Ethylene finds use as a general anesthetic. Some anesthetists believe it is superior to ether, because it is easier for the patient to take and is attended with less postoperative nausea and vomiting. It has little effect on blood pressure, and for this reason, is an excellent anesthetic for nephritic, diabetic, or cardiovascular patients.

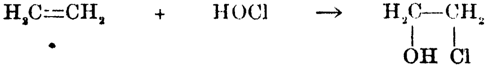
Ethylene has found widespread application in the artificial ripening of fruits and vegetables. It speeds the natural coloring process by causing the disappearance of chlorophyll, the green pigment. At the same time, it hastens the conversion of starch to sugar, and thus aids in making the product like the naturally ripened fruit or vegetable. The treatment does not affect the vitamin content of the products, nor does it impart any undesirable taste or odor.

Many fruits and vegetables have to be picked before they are fully ripe if they are to be satisfactorily packed and shipped any distance. These products, when they arrive near their point of consumption, can be improved in appearance and quality by artificial ripening with ethylene before they are placed on the market. (The consumer is willing to pay more for appearance than for any other quality!) The gas has proved a boon to truck gardeners in the salvaging of tomatoes that have had to be picked green on account of threatened early frost. After treatment with ethylene the tomatoes develop their natural red color. Bananas, because of their extremely perishable nature, are shipped green, and before they are placed on the retail market they are treated with ethylene to cause the development of the attractive yellow color of the tree-ripened fruit. The gas treatment is used to bring a bright orange color to the skins of some types of oranges, which persist in staying green even though the fruit is fully ripe. Still other products that have been successfully treated with ethylene gas are tropical fruits (mangoes, avocados, papayas, custard apples, jùjubes, pineapples), apples, pears, melons, and celery.

Relatively low concentrations of the gas are effective, and the cost of treatment is negligible. For instance, the cost of treating a whole carload of bananas is only about forty cents. The highest concentration required for any product is one part of ethylene to 1,000 parts of air, and concentrations as low as one part to 10,000 parts of air are effective for some products.

Careful work by various investigators, notably Dr. R. B. Harvey and his co-workers at the University of Minnesota, has shown that minute quantities of ethylene are produced by fruits, especially apples, in the natural ripening process. Ethylene treatment is probably mainly a substitute for the process that would normally take place in the course of ripening.

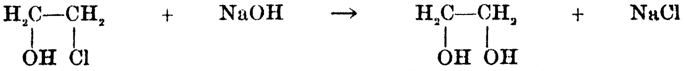
Ethylene is necessary in the manufacture of chlorohydrin, a liquid used in breaking the dormant period of potatoes. Potatoes that have been harvested will not sprout if they are planted immediately, but after treatment with a solution of ethylene chlorohydrin they can be used at once as seed for a second crop.



$$H_2C{=}CH_2 \quad + \quad HOCl \quad \rightarrow \quad \underset{OH}{H_2C}{-}\underset{Cl}{CH_2}$$

Ethylene — Hypochlorous acid — Ethylene chlorohydrin

Another use of ethylene is in the manufacture of ethylene glycol, used as an antifreeze for automobile radiators.



$$\underset{OH}{H_2C}{-}\underset{Cl}{CH_2} \quad + \quad NaOH \quad \rightarrow \quad \underset{OH}{H_2C}{-}\underset{OH}{CH_2} \quad + \quad NaCl$$

Ethylene chlorohydrin — Ethylene glycol or Prestone

Recently the manufacture of ethyl alcohol from ethylene has become an important industrial process (see page 153).

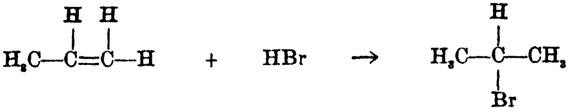
Ethylene is the raw material for the production of polyethylene plastics, which have the trade name *Polythene.* This plastic first was developed in England, and commercial production in the United States did not begin until 1943. It is made by the polymerization of ethylene at pressures of from 500-3000 atmospheres, temperatures of 100-300° C., and with the aid of catalysts such as benzol peroxide or oxygen.

$$n\ CH_2{=}CH_2 \xrightarrow[\text{catalyst}]{\text{high temp. and pressure}} [\text{----}CH_2CH_2\text{----}]_n$$

Ethylene Polyethylene

The polyethylene plastics are semirigid, waxy, translucent solids, which possess such properties as excellent electrical insulation characteristics, chemical inertness, low specific gravity, and low moisture absorption. Polythene is being used as insulation for coaxial television transmission cable. Polyethylene film retains its flexibility at low temperatures. This property has resulted in the adoption of the plastic for deep-freeze packaging. Ice cube trays, tumblers, and cigarette cases are other new applications.

Propylene.—The next higher homologue of ethylene is the gaseous unsaturated hydrocarbon known as propylene. It is obtained industrially as a by-product of the cracking industry, and it occurs also in casing head gas. As in the case of ethylene, its most important chemical reactions are those of addition. The presence of another carbon atom in the molecule, however, adds a different feature to the addition reactions. For example, in the addition of halogen acid, the halogen, which is the negative part of the molecule, combines with the carbon atom holding the smallest number of hydrogen atoms.



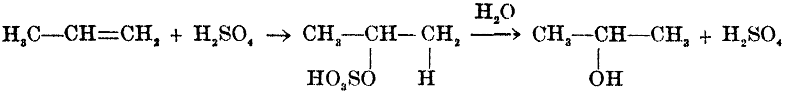
$$H_3C{-}\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}H \quad + \quad HBr \quad \rightarrow \quad H_3C{-}\underset{\underset{Br}{|}}{\overset{H}{\overset{|}{C}}}{-}CH_3$$

Propylene Isopropyl bromide

This particular type of addition was observed by a Russian chemist, Markownikoff, to be a general reaction for unsaturated compounds in which one of the carbon atoms carries fewer hydrogen atoms than the others. The general statement of this type of addition, known as Markownikoff's rule, is that *in the*

addition reactions of unsaturated compounds, the negative part of the adding molecule goes to the carbon atom with the fewest hydrogen atoms.

The operation of this rule is also observed in the addition of sulfuric acid to propylene. This reaction is of industrial importance, for when the propyl hydrogen sulfate formed by the addition of sulfuric acid to propylene is treated with water, isopropyl alcohol is formed.



$$H_3C{-}CH{=}CH_2 + H_2SO_4 \rightarrow \underset{HO_3SO\quad H}{CH_3{-}CH{-}CH_2} \xrightarrow{H_2O} \underset{OH}{CH_3{-}CH{-}CH_3} + H_2SO_4$$

Propylene Isopropyl hydrogen sulfate Isopropyl alcohol

Isopropyl alcohol is a widely used solvent for lacquers, such as those employed in the automobile and airplane industries.

Rather surprisingly, the reaction between propylene and chlorine at high temperatures is that of substitution rather than addition.

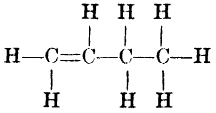
$$CH_2{=}CH{-}CH_3 + Cl_2 \xrightarrow{400\text{-}600^\circ\ C.} CH_2{=}CHCH_2Cl + HCl$$

Propylene 3-Chloropropene or allyl chloride

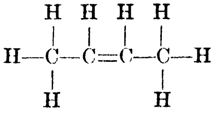
This reaction is of industrial importance because allyl chloride by a series of reactions can be transformed into glycerin, for which there is a great demand.

Butylene.—Butylene is obtained from the same sources as propylene. The equations for the reactions of butylene can be written by reference to those given for propylene, the only difference being that there are an additional carbon atom and two additional hydrogen atoms involved. Large quantities of butylene are used in the preparation of isobutyl alcohol. Before butylene was available from the cracking process, isobutyl alcohol was a laboratory curiosity, but now it is available in tank car lots. The automobile industry consumes large quantities of it as one of the solvents for nitrocellulose lacquers used in automobile finishes.

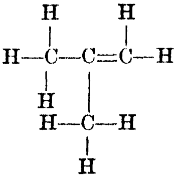
There are three butylenes, or butenes, as compared with two isomeric forms of butane. The presence of the double bond accounts for the additional isomer. Their graphic formulas and I.U.C. names are:



1-Butene

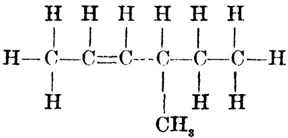


2-Butene

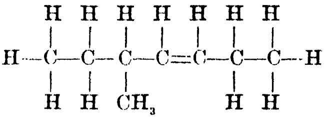


2-Methyl-1-propene

In naming the unsaturated compounds according to the I.U.C. system, the numbering is started from the end of the carbon chain nearest the double bond; in other words, the number indicates the carbon atom at which the double bond starts. The following examples will help to clarify this system of nomenclature:



4-Methyl-2-hexene



5-Methyl-3-heptene

The double bond increases enormously the possibility for isomerism in the members of the olefin series. For example, there are 5 pentenes, 13 hexenes, and 27 heptenes, as compared with 3 pentanes, 5 hexanes, and 9 heptanes in the paraffin series.

Pentenes.—Pentenes, more commonly known as amylenes, are obtained from casing head gasoline and from the cracking process. The Sharples Company has developed a unique industry based on the chlorination of five carbon atom saturated and unsaturated hydrocarbons. The amyl chlorides on hydrolysis give the corresponding alcohols, which, alone or as a mixture, are good solvents.

Acetylene Series.—We will now focus our attention on a class of hydrocarbons that are more highly unsaturated than any thus far considered. The first member of this series, and the only one we shall study in any detail, has the molecular formula C_2H_2, and is known as acetylene. It is the first member of the alkyne or acetylene series of hydrocarbons with the general formula C_nH_{2n-2}. Compounds in this series are either named as derivatives of acetylene or according to the International system with a *yne* ending; thus, the three-carbon member would be called either methyl acetylene or propyne. The *yne* ending is pronounced *ine,* as in line.

Preparation. In 1892 a Canadian, Thomas Willson, while attempting to prepare aluminum in a plant in North Carolina, made an attempt to manufacture metallic calcium by heating lime with carbon. The brittle, dark-colored mass, which evidently was not calcium (in reality it was CaC_2), was discarded as useless. Rain fell on the pile of waste; then a lighted match was carelessly thrown on the dump, with the result that a most violent and spectacular fire ensued. Willson was prompted by this event to turn his attention from aluminum to the production of calcium carbide.

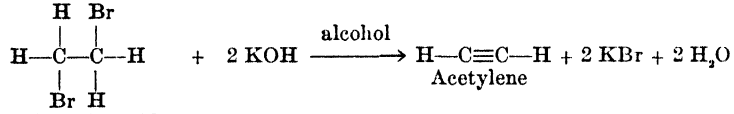
The reaction between calcium carbide and water yields acetylene gas and calcium hydroxide.

$$\underset{\substack{\text{Calcium}\\ \text{carbide}}}{CaC_2} + 2\,H_2O \rightarrow \underset{\text{Acetylene}}{C_2H_2} + \underset{\substack{\text{Calcium}\\ \text{hydroxide}}}{Ca(OH)_2}$$

This is the usual commercial method of preparing acetylene. The calcium carbide is produced by heating a mixture of lime and coke in electric furnaces at a temperature close to 3,000° C.

$$CaO + 3\,C \rightarrow CaC_2 + CO$$

In the laboratory the compound can be prepared from an ethylene halide.



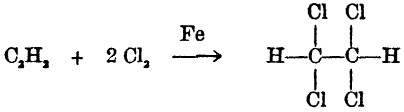
$$\underset{\text{Ethylene bromide}}{H\text{—}\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Br}{|}}{C}}\text{—}\overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}\text{—}H} + 2\,KOH \xrightarrow{\text{alcohol}} \underset{\text{Acetylene}}{H\text{—}C{\equiv}C\text{—}H} + 2\,KBr + 2\,H_2O$$

Ethylene bromide

Physical properties. Acetylene is a colorless gas with a faint garlic-like odor due to impurities. One liter of water will dissolve a liter of the gas. Acetone, however, is an excellent solvent, for under atmospheric conditions one liter will dissolve 25 liters of the gas, and under twelve atmospheres of pressure, 300 liters of acetylene can be absorbed by only one liter of this solvent. Acetylene can be liquefied, but the product is highly explosive in this form; however, the gas can be safely transported when it is dissolved in acetone absorbed on asbestos or other porous material. Use was made of these facts in the manufacture of the portable "Prest-o-lite," a cylinder holding acetylene gas dissolved in acetone and formerly used in the headlights of automobiles and bicycles.

Chemical reactions. Chemically, acetylene is a very active compound, as might be expected from the presence of a triple bond. Like members of the ethylene series, it undergoes a number of addition reactions, some of which are:

1. Acetylene plus chlorine to give tetrachloroethane



$$C_2H_2 + 2\,Cl_2 \xrightarrow{Fe} H-\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{C}}-\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{C}}-H$$

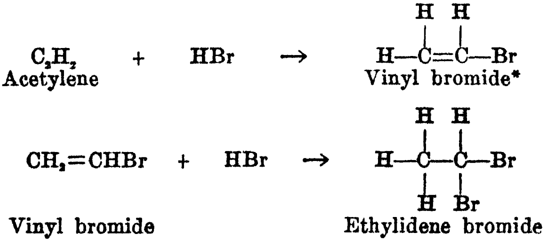
Tetrachloroethane has been shown by preliminary field trials to be effective in the eradication of European bindweed. In many states this plant is considered to be the most serious of weeds, and its immediate eradication is an urgent problem. At the present time, the high cost of tetrachloroethane makes its use for large areas impracticable. Exposure over extended periods to the vapors, as well as contact with the skin, is toxic to man so that care must be exercised in its use.

2. Addition of hydrogen

$$\underset{\text{Acetylene}}{C_2H_2} + 2\,H_2 \xrightarrow{Ni} \underset{\text{Ethane}}{H_3C-CH_3}$$

It will be noted that in this manner a paraffin hydrocarbon (ethane) can be prepared from the highly unsaturated acetylene.

3. Addition of halogen acid



$$\underset{\text{Acetylene}}{C_2H_2} + HBr \rightarrow \underset{\text{Vinyl bromide*}}{H-\overset{\overset{H}{|}}{C}=\overset{\overset{H}{|}}{C}-Br}$$

$$\underset{\text{Vinyl bromide}}{CH_2{=}CHBr} + HBr \rightarrow \underset{\text{Ethylidene bromide}}{H-\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{C}}-\overset{\overset{H}{|}}{\underset{\underset{Br}{|}}{C}}-Br}$$

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[*] The radical $CH_2 = CH-$ is called vinyl.

The student will observe that the second reaction, from which ethylidene bromide is obtained, illustrates the operation of Markownikoff's rule.

Like the other hydrocarbons, acetylene yields carbon dioxide and water on complete combustion. However, because of its molecular structure, an inherent characteristic property of the compound is that it liberates an enormous amount of heat on combustion, thus producing a very hot flame.

$$2\,C_2H_2 + 5\,O_2 \rightarrow 4\,CO_2 + 2\,H_2O + 619{,}700 \text{ calories}$$

When acetylene was first shipped in metal tanks made of copper, or containing any copper in their construction, violent explosions often occurred. Investigation of the cause showed that ammoniacal solutions of certain metallic chlorides, especially those of copper and silver, react with acetylene to form acetylides.

$$\underset{\text{Acetylene}}{C_2H_2} + Cu_2Cl_2 + 2\,NH_4OH \rightarrow \underset{\text{Copper acetylide}}{CuC{\equiv}CCu} + 2\,NH_4Cl + 2\,H_2O$$

Copper acetylide is a solid, which when dry is a very temperamental compound, but so long as it is kept moist it is safe. Explosions, no doubt, were the result of the formation of acetylides in the tanks. This same reaction under controlled conditions can be used in the laboratory for the purification of acetylene, for when the acetylides are treated with dilute acid, acetylene is regenerated.

A reaction of much commercial importance is the formation of acetic acid by the interaction of acetylene and water in the presence of sulfuric acid and mercury salts.

$$\underset{\text{Acetylene}}{C_2H_2} + 2\,H_2SO_4 \xrightarrow{HgSO_4} \underset{\text{Intermediate product}}{[CH_3CH(OSO_3H)_2]} \xrightarrow{+\,H_2O} \underset{\text{Acetaldehyde}}{CH_3CHO} + 2\,H_2SO_4$$

$$\underset{\text{Acetaldehyde}}{CH_3CHO} \xrightarrow[\text{air}]{MnO_2} \underset{\text{Acetic acid}}{CH_3COOH}$$

Acetic acid is the characteristic acid in vinegar, and is also a very important industrial chemical. The foregoing reaction was developed during the first World War for the manufacture of acetic acid, which was one of the substances required for the preparation of "dope" for the fuselage of airplanes.

During the interrogation of German chemists at the close of World War II, it was learned among other things that acetylene was used extensively in Germany's war industries. The chemist largely responsible for this phenomenal development was Walter Reppe. He dispelled the fears of explosion associated with the use of acetylene gas at high pressures and employed this gas on a commercial scale at pressures of 3000 pounds per square inch. Such diverse products as antimalarials, blood substitutes, nylon, and plastics were produced by reactions of acetylene with various substances in the presence of catalysts. It was revealed also that butadiene for the manufacture of synthetic rubber was obtained through a series of reactions beginning with the interaction between acetylene and acetaldehyde or formaldehyde.

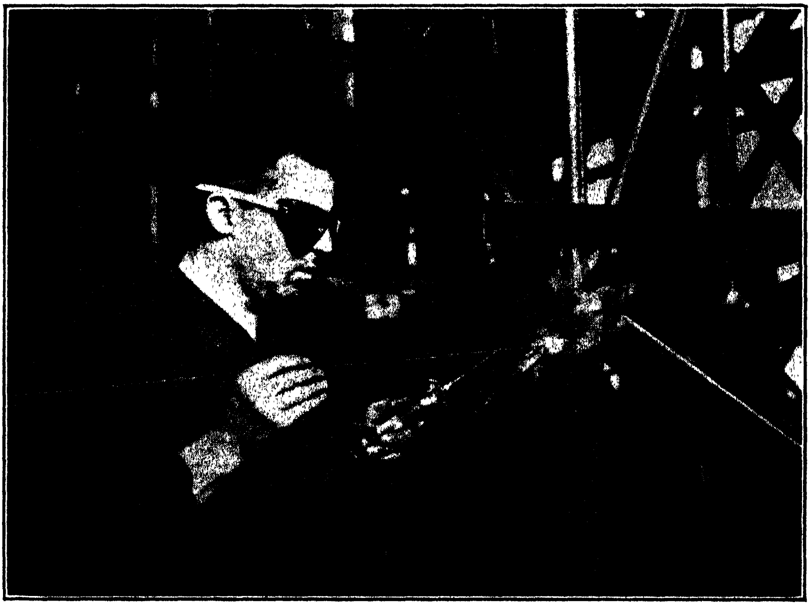
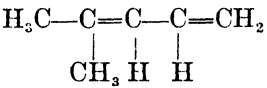


Fig. 19.—An oxyacetylene torch being used to weld an airplane fuselage. The heat from the combustion of acetylene is so great that the ends of metal melt and fuse together at the point of the flame. The long, thin welding rod, which is being fed into the flame, melts and fills the joint. (Courtesy of the Linde Air Products Co.)

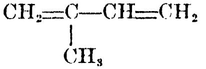
Uses. In addition to the uses of acetylene already mentioned, the gas has a very important use in the oxyacetylene welding torch. The combustion of a mixture of oxygen and acetylene gives an extremely high temperature (about 2,700° C.) that easily liquefies most metals. When the torch is to be used for cutting through thick iron plates, an atmosphere of oxygen is supplied for the combustion, so that the iron not only is melted, but also burns and flies away as sparks, as a result of the excess of oxygen.

Fig. 20.—Heavy steel plates being cut with the oxyacetylene cutting torch at the site where they are to be used. The heat liberated by the combustion of the acetylene melts the steel, and a jet of oxygen rapidly converts the molten iron to iron oxide, which flies away as sparks. (Courtesy of the Linde Air Products Co.)

The use of acetylene in the production of one type of synthetic rubber will be discussed later.

Diolefins or Alkadienes.—The compounds in the diolefin or alkadiene series closely resemble the olefins in character, except that they have two double bonds instead of one. They have the type formula C_nH_{2n-2}. This is the same as that for the acetylene series. The diolefin molecules will add four monovalent atoms, but the addition takes place on four different carbon atoms. In naming the diolefins, the *ne* is dropped from the paraffin name and *diene* is added. The positions of the double bonds are indicated by numbers, as in the case of the olefins. For example,  $H_3C{-}\underset{CH_3}{C}{=}\underset{H}{C}{-}\underset{H}{C}{=}CH_2$ is designated as 4-methyl-1,3-pentadiene.

Important members of this series are isoprene and butadiene.



$CH_2{=}\underset{CH_3}{C}{-}CH{=}CH_2$

Isoprene (2-methylbutadiene-1,3)

$CH_2{=}CH{-}CH{=}CH_2$

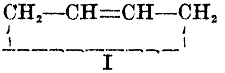
Butadiene-1,3

Compounds that have an arrangement of alternate single and double bonds, such as occurs in isoprene and butadiene, are said to contain *conjugated double bonds.* The increased reactivity of conjugated dienes is important in polymerization reactions such as the production of synthetic rubbers. Addition takes place mainly at the ends of a conjugate system. This is known as 1,4-addition. When this type of addition takes place, a double bond is formed between the center carbon atoms.

$$\underset{\text{Butadiene-1,3}}{CH_2{=}CH{-}CH{=}CH_2} + Br_2 \rightarrow \underset{\substack{\text{1,4 Dibromobutene-2}\\ \text{(1,4-addition product)}}}{BrCH_2{-}CH{=}CH{-}CH_2Br}$$

It is important to remember that 1,4-addition may occur with compounds that have conjugate double bonds, but *not* with dienes that do not contain this arrangement of *alternate* single and double bonds.

The occurrence of 1,4-addition to a conjugate system can be explained by the phenomenon known as *resonance.* This can be considered as a shifting of electrons within the molecule.



$CH_2{-}CH{=}CH{-}CH_2$

I

$CH_2{=}CH{-}CH{=}CH_2$

II

Since the arrangement in which there is a single unpaired electron is unstable, the existence of a bond between atoms 1 and 4 often is indicated by a dotted line connecting them. It is believed that butadiene and similar compounds are not a mixture of isomers, such as I and II, but actually are one substance whose arrangement of electrons cannot be accurately described by either formula. Instead the structures are a sort of hybrid between the two types of structures represented by I and II.

Butadiene. The synthetic rubber program enormously increased the demand for butadiene since it is the principal constituent of the types of elastomers produced in the largest quantities. Butadiene is a gas at room temperatures, boiling at -4.6° C. In the United States butadiene is manufactured from petroleum, natural gas or ethyl alcohol. During World War II about one-third of the total production was derived from alcohol.

Since the C_4 fraction obtained from either natural gas or the products of the cracking process is principally n-butane, the production of butadiene can be illustrated by the following equations:

$$\underset{\text{Butane}}{CH_3{—}CH_2{—}CH_2{—}CH_3} \xrightarrow[\text{high temp.}]{\text{dehydrogeneration, catalyst}} \text{butenes} \xrightarrow[\text{high temp.}]{\text{catalyst, dehydrogenation}} \underset{\text{Butadiene-1,3}}{CH_2{=}CH{—}CH{=}CH_2}$$

The production of butadiene from alcohol involves the catalytic oxidation of the alcohol to acetaldehyde, which is reacted with more alcohol at an elevated temperature in the presence of a catalyst to form butadiene. The following equations indicate the probable course of the reaction.

$$\underset{\text{Ethly alcohol}}{C_2H_5OH} + \text{air} \xrightarrow{\text{catalyst}} \underset{\text{Acetaldehyde}}{CH_3CHO} + H_2O$$

$$CH_3CHO + C_2H_5OH \xrightarrow{\text{catalyst}} \underset{\text{Butadiene-1,3}}{CH_2{=}CH{—}CH{=}CH_2} + 2\ H_2O$$

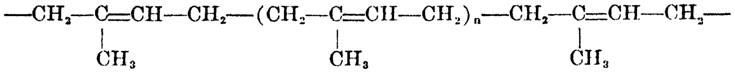
It is probable that the acetaldehyde and alcohol combine to form 1,3-butylene glycol, which loses water to give the butadiene.

To appreciate some of the difficulties involved in the synthetic rubber program it may be noted that butadiene is very inflammable, is toxic, and is very reactive chemically. On standing it is converted slowly to a polymer and must therefore be treated with preservatives and stored under special conditions.

Isoprene. The structural unit of a class of cyclic hydrocarbons known as terpenes is *isoprene.*

These hydrocarbons are the chief components of the essential oils obtained by steam distillation of the sap and tissues of certain plants, particularly those of the coniferous and citrus families. Turpentine and camphor are terpenes, as are also oils of lemon and juniper. Essential oils are important in the preparation of perfumes and drugs.

Natural Rubber.—Another important polymerization product of isoprene is the natural polymer obtained from the latex of the rubber tree, *Hevea brasiliensis.* This latex is a milky emulsion contained in the inner bark and is entirely separate from the sap. It is coagulated with acetic or formic acid, washed with water, and dried to give the crude rubber of commerce. Experimental results indicate that natural rubber is a long chain (linear polymer) composed of isoprene units. A typical portion of the polymer can be represented as follows:



$$—\mathrm{CH_2}—\underset{\mathrm{CH_3}}{\underset{|}{\mathrm{C}}}{=}\mathrm{CH}—\mathrm{CH_2}—(\mathrm{CH_2}—\underset{\mathrm{CH_3}}{\underset{|}{\mathrm{C}}}{=}\mathrm{CH}—\mathrm{CH_2})_n—\mathrm{CH_2}—\underset{\mathrm{CH_3}}{\underset{|}{\mathrm{C}}}{=}\mathrm{CH}—\mathrm{CH_2}—$$

The molecular weight has been estimated as ranging from 100,000 to 400,000, or from 2000 to 6000 isoprene units.

The elasticity of rubber is explained on the theory that there are regions in which the long polymerized isoprene chains are coiled or kinked into a "brush heap" structure. According to this explanation, the stretching of rubber is the uncoiling or straightening of the spiral chains into a parallel arrangement. The recovery of "snap-back" of rubber and other elastomers is thought to be due to the tendency of the molecular chains to revert to their original, coiled, amorphous positions.

Natural rubber as it is shipped from the plantation is not a very useful substance without further chemical transformation. It is elastic but not very tough and cannot be shaped easily into useful articles. Besides being sticky in hot weather and brittle at low temperatures, its tensile strength and resistance to abrasion are low. Natural rubber also is soluble in organic solvents and easily is oxidized by exposure to air. The story of how Charles Goodyear in 1837 accidentally dropped a mixture of rubber and sulfur on a hot stove and then noted the remarkable change in the properties of the rubber often has been referred to as the beginning of the production of satisfactory rubber products. This process is now known as *vulcanization.*

The compounding and vulcanization of rubber is a highly developed, complicated art and science. The first step in the processing of natural rubber is milling or masticating in which the raw rubber is run between steel rollers revolving at different speeds and heated or cooled as desired. This operation softens or plasticizes the rubber to a point where added materials can be milled into it homogeneously. After rubber is softened sufficiently by milling, a wide variety of substances may be added, depending on the ultimate use of the finished product. These substances include accelerators, activators, antioxidants, fillers, pigments, and vulcanizing agents.

The great influence of reinforcing fillers on the final product is well illustrated by the use of carbon black. The effect is to increase enormously the tensile strength and abrasion resistance of the natural product. In the early twenties before the general use of carbon black, tires containing zinc oxide fillers could not be relied upon for more than 3,000 miles of service. With the advent of carbon black as a reinforcing filler and modern methods of compounding, mileages of 30,000 have become commonplace. The effect of adding various carbon black fillers on the abrasion resistance of the butadiene type of synthetic rubbers is even more pronounced than their effect on natural rubber.

Vulcanization, the final step, usually is carrried out by the use of heat and pressure for a controlled and definite period of time. The chemical changes that take place during vulcanization are not well understood, but it is known that sulfur reacts with the rubber hydrocarbon, possibly to give a certain amount of cross linking of sulfur between the isoprene chains.

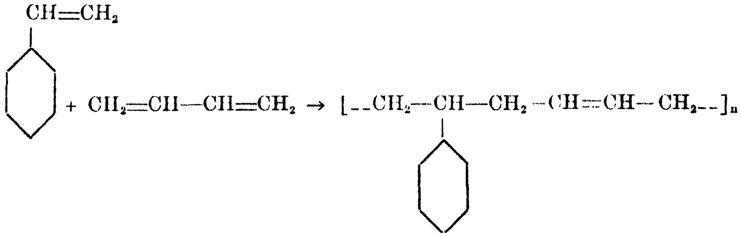
Synthetic Rubber.—Synthetic rubbers became of great importance after the sudden cessation in 1942 of imports of the natural product from the Far East Indies. Rubber long had been recognized as a vulnerable spot in America's economic and defense structure. The United States, with 68 per cent of the world's motor vehicles, had used about one-half the annual world production of rubber, or, normally, about 600,000 tons. About 98 per cent of this came from British Malaya and the Dutch East Indies. During 1941 increased use of rubber due to defense preparations and civilian demands raised the domestic consumption of rubber to an estimated total of 740,000 tons. In normal times 70 to 80 per cent of the rubber consumption of the United States is used in the manufacture of automobile

Fig. 21.—Neoprene chemical rubber being discharged from the kettle in which it was made by the polymerization of chloroprene, an acetylene derivative. At this stage it is similar in appearance to coagulated latex from the rubber tree, and will be ready for use after washing and drying. (Courtesy of the Du Pont Co.)

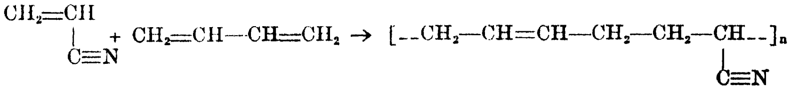
TABLE IX

UNITED STATES SYNTHETIC RUBBERS*

MONOMERS POLYMER

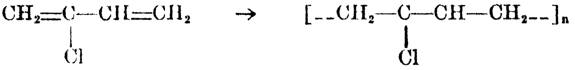


Styrene Butadiene Buna S, GR-S



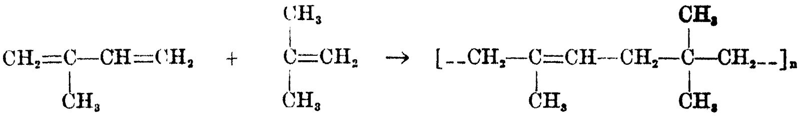
$$\underset{\overset{|}{C\equiv N}}{CH_2{=}CH} + CH_2{=}CH{-}CH{=}CH_2 \rightarrow [\,{-}{-}CH_2{-}CH{=}CH{-}CH_2{-}CH_2{-}\underset{\overset{|}{C\equiv N}}{CH}{-}{-}\,]_n$$

Acrylonitrile Butadiene Buna N, GR-N, Chemigum



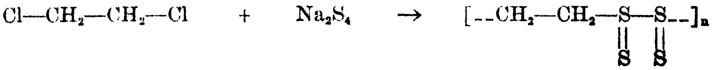
$$CH_2{=}\underset{\overset{|}{Cl}}{C}{-}CH{=}CH_2 \rightarrow [\,{-}{-}CH_2{-}\underset{\overset{|}{Cl}}{C}{-}CH{-}CH_2{-}{-}\,]_n$$

Chloroprene Neoprene, GR-M



$$CH_2{=}\underset{\overset{|}{CH_3}}{C}{-}CH{=}CH_2 + \overset{\underset{|}{CH_3}}{\underset{\overset{|}{CH_3}}{C}}{=}CH_2 \rightarrow [\,{-}{-}CH_2{-}\underset{\overset{|}{CH_3}}{C}{=}CH{-}CH_2{-}\overset{\underset{|}{CH_3}}{\underset{\overset{|}{CH_3}}{C}}{-}CH_2{-}{-}\,]_n$$

Isoprene Isobutylene Butyl, GR-I



$$Cl{-}CH_2{-}CH_2{-}Cl + Na_2S_4 \rightarrow [\,{-}{-}CH_2{-}CH_2{-}\underset{\overset{\|}{S}}{S}{-}\underset{\overset{\|}{S}}{S}{-}{-}\,]_n$$

Ethylene dichloride Sodium tetrasulfide Thiokol, GR-P

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*The term *elastomers* also has been applied to this class of rubber-like substances. Strictly speaking, the term "synthetic rubbers" is incorrect, because these polymeric rubber-like substances do not have the same molecular configuration as natural rubber. In the absence of any accepted system of nomenclature, however, the term "synthetic rubbers" has been applied to these substances that possess the physical properties of natural rubber.

tires. But rubber is a vital material for many purposes other than the manufacture of tires. Shreve states that rubber is fabricated into 30,000 different articles. Mechanical rubber goods, such as belting, packing, and mounting for engines, normally use about 10 per cent of the annual rubber consumption

A.

Fig. 22.—*A*, Household articles, such as the sink strainer and scraper, are now being made of neoprene. These articles give long service because they resist deterioration by greasy substances with which they come in daily contact. In addition, neoprene replaces natural rubber for many industrial uses because of its resistance to oils and organic solvents. *B*, Household gloves made of neoprene are long lived, because they are little affected by the action of oils and grease. (Courtesy of Du Pont Style News Service and the Du Pont Co.)

of the United States. About 6 per cent is manufactured into such articles as rubber footwear, heels, soles, and raincoats; and the uses of rubber as an electrical insulating material account for 4 per cent. Another 5 per cent is consumed in making a myriad of familiar articles such as floor mats, bathing caps, and athletic equipment.

B.

Prior to 1942 the amount of synthetic rubber produced in the United States was only about 1.5 per cent of the normal annual importation of natural rubber. When the supply of natural rubber was cut off suddenly, an entirely different situation developed with regard to synthetic rubber. Almost overnight the position of synthetic rubber as a product made for special purposes was transformed into one of almost entirely replacing natural rubber. If the atomic bomb project is excluded, the synthetic rubber program is probably the greatest organic chemical and chemical engineering program ever attempted. America's achievement in meeting its rubber requirements is all the more remarkable when it is realized that from a total synthetic rubber production of 25,000 tons in 1942 the production skyrocketed to 800,000 tons in 1944.

The five principal types of synthetic rubbers or elastomers produced during the late war and still in production will be discussed briefly. The molecules, called the "monomers," that are polymerized to form the various types of synthetic rubbers are shown in Table IX. A typical portion or segment of the polymer chain also is given.

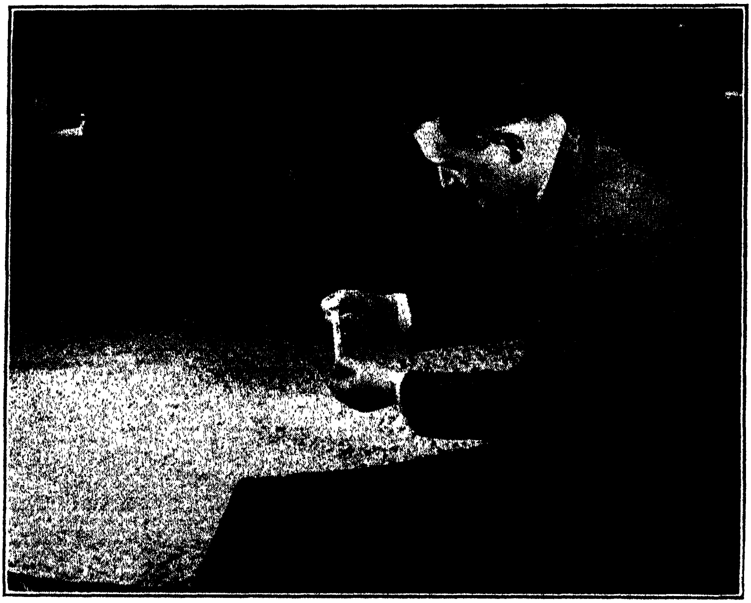

Fig. 23.—A step in the manufacture of Hycar, which is made by the polymerization of butadiene, a petroleum product. The curds of synthetic latex have been coagulated with acid. After washing, the cruds are skimmed from the vat and made into blocks of raw synthetic rubber. (Courtesy of the B. F. Goodrich Co.)

GR-S. The type of synthetic rubber produced in the largest quantity is made by the copolymerization of the monomers, butadiene, and styrene. The process, according to a U. S. patent disclosure, consists in preparing the synthetic rubber latex by polymerizing a mixture of 75 parts of butadiene and 25 parts of styrene in an aqueous emulsion containing 180 parts of water, 5 parts of fatty acid soap as an emulsifying agent, 0.3 part of potassium persulfate as a polymerization initiator, and 0.6 part of a mixture predominantly dodecylmercaptan as a polymerization modifier. The entire reaction mixture is kept at a temperature of 50° C. for 14 hours, after which 0.2 part of β-naphthol is added to stop polymerization. At this time about 70 per cent of the monomers have been converted into the synthetic rubber polymer. After removal of the untreated butadiene and styrene, the latter is pumped to blending tanks where the various batches are mixed to form a uniform product and where about 1.5 per cent phenyl-β-naphthyl amine is added as an antioxidant. From the blending tanks the latex is pumped to a wooden creaming tank where brine is added to flocculate the rubber particles. Next it goes to the coagulation tank and the soap-conversion tank where acid is added and soap converted into fatty acid. After filtration, washing, and drying, the synthetic product is compressed into 75 pound blocks for shipment to rubber factories to be used for processing into finished articles.

This type of synthetic rubber can be processed in the machines used for natural rubber, but it requires more severe milling. Properly compounded GR-S is similar to natural rubber in most properties such as elasticity, tensile strength, and abrasion resistance. It is superior to natural rubber in resistance to aging, and has a lower permeability to gases. However, it has the disadvantage of inferior rebound and high heat generation so that it is not very satisfactory for use in heavy truck tires.

GR-N (Perbunan). This type of synthetic elastomer is a copolymer of butadiene and acrylonitrile. The ratio of the monomers is about 3:1, and the method of obtaining the product is very nearly the same as for the GR-S process. The outstanding characteristic of GR-N is its resistance to oils, solvents, and chemical agents. These properties make it useful in the manufacture of carburetor diaphragms, aircraft hoses, and printing rolls. Other applications are large size hoses for handling oil, gasoline hoses for service station pumps, and for shoe soles.

Neoprene (GR-M) (Polychloroprene). The elastomer that was produced in the largest amount before the urgent need for rubber substitutes arose was the one obtained from acetylene. Most of the fundamental research on this process was done by the late Professor Nieuwland and his associates at Notre Dame University. He found that when acetylene was passed through a concentrated solution of cuprous chloride and ammonium chloride, monovinyl acetylene was formed, which, upon the addition of hydrogen chloride gas, yielded chloroprene. In the presence of zinc oxide and amines or other catalysts, chloroprene polymerizes to a pale yellow elastic mass termed "Neoprene" by the Du Pont Company, which has developed Nieuwland's patents. It will be noted that chloroprene corresponds to isoprene except for the substitution of chlorine for the methyl group in isoprene.

$$\underset{\text{Acetylene}}{2\ HC{\equiv}CH} \xrightarrow[NH_4Cl]{CuCl_2} \underset{\text{Monovinyl acetylene}}{HC{\equiv}C{-}CH{=}CH_2}$$

$$HC{\equiv}C{-}CH{=}CH_2 + HCl \rightarrow \underset{\text{Chloroprene}}{CH_2{=}CCl{-}CH{=}CH_2}$$

Neoprene is similar to natural rubber in most of its properties, but it is greatly superior in its resistance to sunlight, atmospheric oxygen, heat, oil, solvents, and chemicals. Gloves made from Neoprene are superior to rubber gloves for household tasks, such as dry cleaning, furniture polishing, and painting, since ordinary rubber gloves soon swell and disintegrate when in contact with solvents and oils. Large hoses, such as those used on tankers, often are made of Neoprene. Another use is for lining storage tanks for gasoline and other petroleum chemicals.

Butyl Rubber (GR-I). This type of rubber is a result of a desire to produce a "tailor made" rubber with specific properties. It is manufactured by the low temperature copolymerization of isobutylene and a diene, usually isoprene. Only a small percentage of diolefin is used so that the final product has only just sufficient unsaturation to permit vulcanization. Isobutylene and isoprene are mixed, cooled to –46° C., and fed into the reaction tank where the reaction is carried out at approximately the same temperature. The amount of conversion of isobutylene to butyl rubber is controlled by the amount of catalyst introduced into the bottom of the reacting mixture. After removal of the unconverted monomers, the product is dried and boxed for shipment.

Because the relative amounts of isobutylene and isoprene are controlled, the product contains only 1 or 2 per cent of the unsaturation present in natural rubber; hence the product is relatively inert chemically. This makes it superior to natural rubber for many purposes. It is resistant to acid, has high heat resistance, and is highly impermeable to air and gases, such as hydrogen, helium, and carbon dioxide. Butyl rubber is well adapted to the fabrication of inner tubes for tires because of its ability to prevent diffusion of air and also because of its excellent tear-resistant properties.

Since butyl rubber is soluble in gasoline and other paraffin hydrocarbons, it is especially suitable for use in cements and coating compositions. The toxic aromatic hydrocarbons, such as benzene, commonly employed as a solvent for natural rubber in such products thus can be avoided. Other applications of butyl rubber are for use in fire and air hoses, electrical insulation, ballon fabrics, gas masks, and pontoons.

Thiokols. The synthetic elastomers obtained by the condensation polymerization of dihalides and sodium tetrasulfide are known as Thiokols. The reaction involves the loss of sodium chloride and the linking of the hydrocarbon and polysulfide groups into long chains. There are several types of Thiokols depending on the raw materials used. The one obtained from ethylene dichloride and sodium tetrasulfide is called Thiokol-A. If a mixture of ethylene dichloride and propylene dichloride is used instead of ethylene chloride alone, the product is known as Thiokol-N. The raw materials for the manufacture of Thiokols are inexpensive and plentiful. Sodium tetrasulfide is made from sodium sulfide and sulfur. Ethylene dichloride is produced by the reaction of ethylene (a refinery by-product) and chlorine from ordinary salt. The polymerization reaction is carried out by the emulsion method using magnesium hydroxide to emulsify the ethylene dichloride.

This is the only one of the synthetic rubbers that differs radically in structure from natural rubber. The structure of its long chain polymer is shown in Table IX. There is considerable difference in reactivity of the sulfur atoms, two being fairly readily removed by treatment with NaOH.

The Thiokols have some very desirable as well as some disagreeable properties. They are unequaled in resistance to solvents, such as hydrocarbons, ether, alcohol, and many other organic solvents. Their strength is little affected by prolonged immersion in solvents that are injurious to natural rubber. The chief disadvantage is that most varieties possess a disagreeable odor, exhibit cold flow, and have low abrasive resistance and poor heat resistance. The most important uses of Thiokols are based on their solvent resistance and impermeability to gases. They are utilized in gaskets, printers' rolls, and hoses of all types for use in contact with solvents. Large underground concrete storage tanks for gasoline have been lined successfully with this material.

Thiokol was used as the gasoline-resistant lining in bulletproof tanks for airplanes and other military equipment. The principle of the self-sealing gasoline tank was to have this inner lining of a gasoline-resistant synthetic, an intermediate layer of nonresistant spongy rubber, and a cover of rubber and fabric. When the tank was pierced by a bullet, gasoline leaked through the hole in the synthetic layer, attacked the nonresistant layer, which swelled and closed the hole.

The synthetic rubbers have established a well-deserved place for themselves. For many uses they are the equal of natural rubber, and they have some applications for which natural rubber cannot be used at all. Another advantage is that the continued production of American synthetic rubber at near capacity or even the use of one-third of capacity with the remaining plants in a stand-by condition, will stabilize the world price of natural rubber. The importance of this is realized when it is considered that the price of natural rubber has varied from an all-time high of $3.12 a pound in 1910 to $1.21 per pound in 1925 and then to a low of 3 cents a pound in 1932.

Study Questions

1. Give three names for the series of unsaturated hydrocarbons of which ethylene is the first member. What is the type formula for this series?
2. Outline the procedure for proving the graphic formula of ethylene.
3. Make a list of the compounds encountered thus far that are obtained from the cracking of petroleum.
4. What is the most important type of reaction of ethylene? Write several typical equations illustrating your answer.
5. What simple test could be used to distinguish ethylene from ethane?
6. List four uses of ethylene.
7. What is Markownikoff's rule? Give an equation to illustrate its operation.
8. Write structural formulas for all the possible amylenes and name them according to the I.U.C. system.
9. Write the graphic formula for 2,4,4'-trimethylhexane.
10. Write an equation representing the formation of acetylene from calcium carbide and water.
11. Write an equation to show the formation of acetic acid from acetylene.
12. What are some of the raw materials used in the preparation of synthetic rubbers?
13. What advantages do the various kinds of synthetic rubber possess over natural rubber?
14. To what class of unsaturated compounds does isoprene belong? What is the importance of this compound?
15. Write an equation to illustrate 1,4-addition to congugated double bonds.

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CHAPTER VI

ALCOHOLS

Introduction.—Alcohols can be considered as hydrocarbons in which one or more of the hydrogens is replaced by an hydroxy or hydroxyl group (-OH). Their wide variety of uses makes them familiar to the layman as well as to the chemist, and both groups would find it exceedingly difficult to do without alcohols.

Methyl Alcohol

Structure of Methyl Alcohol.—In order to illustrate to the student how the graphic formula of an organic compound is established, and especially to enable him to understand better the structure of this important class of compounds, we shall outline the procedure used to establish the structure of the simplest alcohol.

Let us suppose that we have separated by fractional distillation one compound from a wood distillate. We can be fairly certain that we have only one compound if it boils at one temperature, or over a range of not more than one or two degrees. This is one criterion of the purity of a liquid.

Assuming that we know nothing of the compound, it is necessary to make a qualitative analysis for the elements in it. One test is that of ignition. The gases resulting from combustion are passed into limewater, and are found to form a precipitate. This is a positive test for carbon dioxide, which is formed by the burning of carbon; thus we are justified in assuming that the compound contains carbon.

Droplets of water are found to condense out on a cold beaker held just above the flame of the burning compound. This water results from the combustion of hydrogen present in the compound.

A small quantity of the unknown substance then is dropped on hot metallic sodium. This mass is added to water, and tests that show the absence of sulfur, nitrogen, and halogens are made on the filtrate. The absence of a residue on ignition of the compound shows the absence of metallic salts.

The presence of oxygen in a compound is not easy to demonstrate. One fairly accurate test, however, depends on the finding that a solution of iodine in oxygen-free liquids is violet in color, while the iodine solution possesses a brownish tint in liquids containing oxygen. This test is made on the unknown substance. The result indicates that oxygen is present in the molecule.

As a result of these tests, we can assume that the compound contains only carbon, hydrogen, and oxygen.

Now it is necessary to proceed to a quantitative determination of the elements present in the compound. The percentage of carbon in a compound is determined by the complete combustion of a carefully weighed sample in an atmosphere of oxygen. The gases formed are first passed through a dehydrating agent to take out water. The absorption apparatus is weighed carefully before and after the operation. The amount of water formed is determined, and from this the percentage of hydrogen in the sample can be calculated.

Similarly, the increase in the weight of an absorber containing potassium hydroxide gives the weight of carbon dioxide formed. From this quantity the percentage of carbon in the sample can be calculated. The percentage of oxygen is determined by the difference.

The results of such an analysis for our unknown compound are:

$$\begin{array}{lll}
\mathrm{C} = 37.46 \text{ per cent} & (\div 12 = & 3.12 \div 3.12 = 1) \\
\mathrm{H} = 12.59 \text{ per cent} & (\div 1 = & 12.59 \div 3.12 = 4) \\
\mathrm{O} = 49.95 \text{ per cent} & (\div 16 = & 3.12 \div 3.12 = 1)
\end{array}$$

As the calculations show, if the percentages of the elements are divided by their respective atomic weights, we obtain numbers that represent the relative proportions of the elements in the compound. If these quantities are divided by the smallest one of the series, and the quotients are expressed by the nearest whole number, the results show the relative number of atoms of the different elements in the molecule. ***The formula that shows the relative number of atoms in a molecule is known as an empirical formula.*** For our unknown compound the empirical formula is CH_4O.

It is necessary now to make a molecular weight determination to ascertain whether or not the compound is composed of some multiple of this empirical formula. Such a determination gives the value 32; and if we add the atomic weights in our empirical formula, we find that they also total 32. Thus the empirical formula is also the molecular formula of our unknown substance.

The molecular formula shows the total number of the various kinds of atom in the compound, but a graphic formula is necessary to show the spatial arrangement of these atoms. To establish the graphic formula for an unknown compound, it is necessary to resort to chemical reactions.

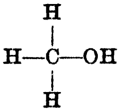
Of course, if we were examining our unknown substance in the laboratory for the first time, it would be necessary to investigate a number of chemical reactions. To shorten our discussion, we shall assume that we already have discovered the most significant reactions. Our compound is found to react with sodium, resulting in the evolution of hydrogen.

$$CH_4O + Na \rightarrow CH_3ONa + [H]^*$$

This reaction demonstrates that one of the hydrogen atoms must be linked in the molecule in a fashion different from the others, for only one hydrogen atom can be replaced by a sodium atom.

If we treat our unknown compound with hydrogen iodide, we find that one atom of iodine replaces one atom of hydrogen and one atom of oxygen. Oxygen is divalent and hydrogen is monovalent; thus, if the monovalent iodine is to replace both the hydrogen and the oxygen, the hydrogen and the oxygen must be present in the form of a monovalent hydroxyl (-OH) group.

Remembering that carbon normally has a valence of 4, oxygen of 2, and hydrogen of 1, we can now write the graphic formula for our unknown compound as:



$$\begin{array}{c} \mathrm{H} \\ | \\ \mathrm{H—C—OH} \\ | \\ \mathrm{H} \end{array}$$

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[*] The student will recall that the hydrogen atom in the reaction will not remain as such, but will combine with another hydrogen atom to form a molecule of hydrogen gas, H_2.

The name of the compound is wood alcohol or methyl alcohol. It is the first member of an homologous series of compounds known as alcohols. *The type formula for all alcohols is ROH.*

Methyl alcohol is the simplest alcohol, and is known variously as wood alcohol, carbinol, wood spirit, or by its I.U.C. name, methanol. According to the International system, alcohols are named by replacing the *e* ending of the paraffin hydrocarbon names by *ol.* Methyl alcohol is not found free in nature, but it occurs in the combined state as an important constituent of many natural products, such as oil of wintergreen and pectin.

Preparation of Methyl Alcohol.—Methyl alcohol can be prepared by heating hard wood in a closed iron retort until all the volatile matter is expelled and a residue of wood charcoal is left. About one-fourth of the wood is recovered as charcoal; another one-fourth is converted to gases, largely methane, which are collected and used subsequently as fuel for the process. The remaining one-half forms a tar and water solution, termed pyroligneous acid. The aqueous solution contains about 3 per cent wood alcohol, 8 to 10 per cent acetic acid, and 0.5 per cent acetone. The acetic acid is neutralized by the addition of lime, forming calcium acetate, which is nonvolatile. The methyl alcohol then is separated by fractional distillation. Because the compound was first obtained by this method of manufacture, it came to be called wood alcohol or wood spirit.

Cheaper synthetic methods have now largely displaced the manufacture of methyl alcohol by the destructive distillation of wood. In 1923 there appeared on the New York market large quantities of methyl alcohol, offered for sale at about one-half the domestic price. This alcohol came from Germany, where it had been made by a secret process. It soon became known that the process consisted of the hydrogenation of carbon monoxide at high temperature and pressure, and in the presence of a special catalyst, to form methyl alcohol.

$$\underset{\substack{\text{Carbon}\\ \text{monoxide}}}{CO} + 2\,H_2 \xrightarrow[\substack{\text{catalysts}\\ \text{250 atmospheres}\\ \text{pressure}}]{300^\circ\text{ C.}} \underset{\substack{\text{Methyl}\\ \text{alcohol}}}{CH_3OH}$$

"Water gas," as the mixture of hydrogen and carbon monoxide necessary for the reaction is called, can be obtained readily and cheaply by passing water vapor over hot coke.

$$H_2O + \underset{\text{Coke}}{C} \rightarrow \underset{\text{Water gas}}{H_2 + CO}$$

The excess hydrogen needed for the reaction is supplied by the electrolysis of water.

This method is of added interest since by varying the temperature, pressure, and catalysts used, it is possible to obtain a wide variety of compounds. One blended mixture known as "synthol," obtained by this method, has been shown to be suitable for use as a motor fuel.

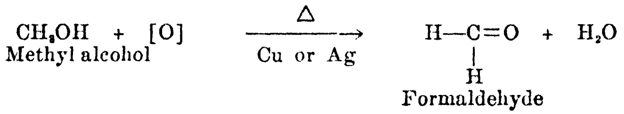
Another synthetic method for the preparation of methanol utilizes carbon dioxide and hydrogen. The carbon dioxide in a high state of purity is obtained as a by-product of the fermentation industries during the production of butyl and ethyl alcohols.

$$\underset{\text{Carbon dioxide}}{CO_2} + \underset{\text{Hydrogen}}{3\,H_2} \overset{\text{catalysts}}{\rightleftarrows} \underset{\text{Methyl alcohol}}{CH_3OH} + H_2O$$

The importance of synthetic methanol as a chemical in the United States can be judged when it is known that in 1946 there were 66,157,000 gallons manufactured, as compared with 31,606,320 gallons in 1937. Of the 1946 production, approximately 97 per cent was synthetic.

Methyl alcohol is a colorless liquid that boils at 64.7° C. It is miscible with water in all proportions. It is a very poisonous compound; ingestion of as little as 10 cc. may cause blindness, and larger quantities can cause death. Its vapors tend to have a destructive effect on the optic nerve. For this reason, it is undesirable to use wood alcohol as an antifreeze in automobile radiators. As the temperature of the engine rises, the alcohol tends to vaporize, and the fumes formed are blown back into the car and are inhaled by the occupants.

Chemical Properties.—Much of the methyl alcohol of commerce is oxidized to formaldehyde by the use of moderate heating in the presence of copper or silver gauze as a catalyst. The formaldehyde thus formed is an important component of certain types of plastics and resins. Formaldehyde also is used in biological and zoological laboratories for preserving specimens.



$$\underset{\text{Methyl alcohol}}{CH_3OH} + [O] \xrightarrow[\text{Cu or Ag}]{\Delta} \underset{\text{Formaldehyde}}{H{-}\underset{\underset{\displaystyle H}{|}}{C}{=}O} + H_2O$$

More vigorous oxidation of methyl alcohol converts the compound to formic acid, and finally to carbon dioxide and water. Both formaldehyde and formic acid will be discussed in more detail in later chapters.

$$\underset{\text{Methyl alcohol}}{CH_3OH} \xrightarrow{[O]} \underset{\text{Formic acid}}{HCOOH} \xrightarrow{[O]} CO_2 + H_2O$$

With acids, methanol reacts to form compounds known as methyl esters.

$$\underset{\text{Methyl alcohol}}{CH_3OH} + \underset{\text{Acetic acid}}{CH_3COOH} \rightarrow \underset{\text{Methyl acetate}}{CH_3COOCH_3} + H_2O$$

Uses.—Methyl alcohol is one of the common denaturants used for making ethyl alcohol unsuitable for beverage purposes. and thus eliminating the high government tax on beverage alcohol. Methanol is used also as a solvent for shellacs, varnishes, and lacquers. It still is sold sometimes as an antifreeze for automobile radiators, but the disadvantage of using wood alcohol for this purpose has been pointed out. Since it is a very reactive compound, it is used as the starting material for a large number of organic syntheses involving the methyl radical. On occasions it is used as a fuel for racing automobiles.

Ethyl Alcohol

Ethyl alcohol, C_2H_5OH, is the two-carbon homologue of methanol. It is called ethanol, grain alcohol, methyl carbinol, or spirit of wine. It is the alcohol found in alcoholic beverages, and is the product meant when the unqualified term *alcohol* is used. Its exhilarating effects have been known since earliest times. Relics found in the tombs of the Pharaohs indicate that fermented beverages were made at that time.

Preparation.—At the present time about one-third of the ethyl alcohol of commerce is made by the fermentation of blackstrap molasses, the residue left after the crystallization of cane sugar. Yeast is added to a solution of molasses, and enzymes, which are organic catalysts (page 581), in the yeast convert the material to alcohol and carbon dioxide.

$$\underset{\text{A sugar}}{C_6H_{12}O_6} \xrightarrow{\text{enzyme}} \underset{\text{Ethyl alcohol}}{2\,C_2H_5OH} + 2\,CO_2$$

The carbon dioxide resulting from the fermentation process is used in the manufacture of dry ice and in the production of synthetic methyl alcohol.

Starch from materials such as corn, barley, wheat, or potatoes also can be used as a starting material for the manufacture of ethyl alcohol. In this process, malted barley is added to the starch material so that the enzymes in the "malt" can convert the starch to a kind of sugar. Then yeast is added, and the sugar is converted to ethyl alcohol and carbon dioxide.

The concentration of alcohol in the fermented masses very seldom exceeds 15 per cent, and a process of fractional distillation is necessary to purify and concentrate the alcohol.

Another means of preparing ethyl alcohol that has developed rapidly in the past decade is the treatment of ethylene with concentrated sulfuric acid, followed by hydrolysis.

$$\underset{\text{Ethylene}}{C_2H_4} + \underset{\substack{\text{Sulfuric}\\\text{acid}}}{H_2SO_4} \rightarrow \underset{\substack{\text{Ethyl hydrogen}\\\text{sulfate}}}{C_2H_5HSO_4} \xrightarrow{\text{hydrolysis}} \underset{\substack{\text{Ethyl}\\\text{alcohol}}}{C_2H_5OH} + H_2SO_4$$

Another important future source of ethyl alcohol probably will be natural gas, utilizing an adaptation of the Fischer-Tropsch process. This process, first used in Germany for the production of synthetic petroleum products from water gas, employed a fixed cobalt-thoria catalyst. It has been made commercially feasible in this country by using the fluid catalyst principle and an iron-containing catalyst. The products obtained from the process will be gasoline, Diesel oil, and a mixture of oxidized compounds including alcohols, acids, ketones, and aldehydes. It has been estimated that the production of these compounds in the Fischer-Tropsch plants may exceed 300,000,000 pounds annually, of which ethyl alcohol will be the chief product. Two plants employing this process are expected to be completed in 1948-1949.

Commercial alcohol is seldom more than 95 per cent pure. This is true since alcohol and water form a constant-boiling mixture containing 95 per cent alcohol; hence, 95 per cent is as high a concentration of alcohol as can be obtained by fractional distillation. Absolute, or 100 per cent alcohol, can be prepared on a small scale by allowing one part of 95 per cent alcohol to stand with three parts of quicklime (calcium oxide). The absolute alcohol then is distilled into a flask provided with a calcium chloride tube to protect it from contact with moist air. On a commercial scale the water is removed from 95 per cent alcohol by distilling the mixture with benzene.

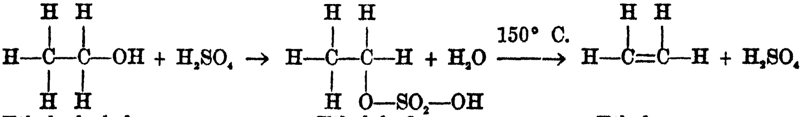
Chemical Properties.—Ethyl alcohol under mild oxidizing conditions yields acetaldehyde. Under similar conditions methyl alcohol gives formaldehyde. This formation of aldehydes is a general type of reaction for all alcohols belonging to the same series as methyl and ethyl alcohol.

$$\underset{\text{Ethyl alcohol}}{C_2H_5OH} \xrightarrow{[O]} \underset{\text{Acetaldehyde}}{CH_3CHO} + H_2O$$

As do all alcohols, ethyl alcohol forms carbon dioxide and water on complete combustion with an adequate supply of oxygen.

$$\underset{\text{Ethyl alcohol}}{C_2H_5OH} + 3\,O_2 \rightarrow 2\,CO_2 + 3\,H_2O$$

Ethyl alcohol reacts with iodine in an alkaline solution to give iodoform (see page 110). This reaction is used as a test for ethyl alcohol because the iodoform is a yellow, crystalline substance with an easily recognizable odor.



$$H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-OH + H_2SO_4 \rightarrow H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{O-SO_2-OH}{C}}-H + H_2O \xrightarrow{150°\ C.} H-\overset{H}{C}=\overset{H}{C}-H + H_2SO_4$$

Ethyl alcohol — Ethyl hydrogen sulfate — Ethylene

The dehydration of ethyl alcohol yields an unsaturated hydrocarbon. This type of reaction is common to all alcohols containing more than one carbon atom.

The temperature for the conversion of ethyl hydrogen sulfate to ethylene must be carefully controlled; otherwise diethyl ether instead of ethylene will form.

Uses.—Ethyl alcohol is used for a great variety of purposes.

1. It is the principal component of many pharmaceuticals. The term "tincture" signifies that a nonvolatile active principle is dissolved in ethyl alcohol. For example, tincture of iodine is prepared by dissolving 2 grams of iodine and 2.4 grams of sodium iodide in enough alcohol-water mixture (50 per cent alcohol by volume) to make 100 cc.

2. Many flavoring extracts commonly used in the home contain alcohol. Vanilla extract is about a 40 per cent alcoholic solution of the vanilla bean.

3. Most perfumes contain alcohol as the principal solvent.

4. The compound is used in large quantities in hospitals as a germicide. A 70 per cent solution has been found to be most effective for this purpose. Most rubbing compounds used in hospitals to soothe and cool the skin contain alcohol as the main component.

5. Denatured ethyl alcohol is probably the most widely used antifreeze compound for automobile radiators. The only disadvantage of ethyl alcohol for this purpose is that it must be replaced frequently because of its relatively low boiling point.

6. Alcoholic beverages contain different amounts of ethyl alcohol. Beer, for example, contains 2 to 10 per cent, wine 7 to 20 per cent, and rum 40 to 50 per cent alcohol.

7. Since ethyl alcohol is a common substance that is readily obtainable, it is the starting material for a large number of chemical syntheses. It is used in the manufacture of ethylene, ether, acetic acid, ethyl chloride, and other ethyl halides.

8. Alcohol burns readily and is used as a fuel. "Canned heat" is a gelatinous mass formed from a mixture of alcohol, nitrocellulose, and soap. There has been considerable agitation

for the use of alcohol in gasoline as a motor fuel. This use is now very common in Europe where there is a shortage of gasoline. One of the principal deterrents to the use of alcohol in gasoline is that the alcohol must be 100 per cent pure. The presence of a small amount of water will cause the gasoline-alcohol blend to separate into two layers. It is difficult to keep gasoline entirely free from water since small amounts are formed in storage or automobile tanks by condensation of moisture in the air due to changes in temperature.

9. A large proportion of the butadiene for the synthetic rubber program in 1943-1945 came from ethyl alcohol. At wartime peak, synthetic rubber production alone took 330 million gallons of alcohol per year and other outlets required 270 million gallons.

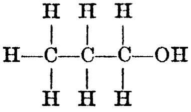
Denatured Alcohol.—Alcohol that is sold for beverage purposes is subject to federal, state, and local taxes. Because of these high taxes the cost of alcohol usually is far above its cost of actual manufacture. However, if alcohol is rendered unfit for beverage purposes by the addition of certain substances, it is not subject to these taxes. Alcohol so treated is known as *denatured alcohol.* Ninety-five per cent beverage alcohol can sell for as much as $18.00 a gallon, whereas the price of the denatured alcohol is about one dollar a gallon. Some manufacturers buy alcohol in tank car lots of 8,000 to 10,000 gallons. When one considers the magnitude of the difference in cost between beverage and denatured alcohol for this quantity, it is easy to understand why industry is interested in denaturing alcohol. It explains also why the official list of the Bureau of Internal Revenue approves such a large number (68) of substances that can be used for denaturing purposes. Because certain denaturants would interfere with a chemical process, industries are allowed by the government to select a substance from the approved list that will not interfere with its use in a particular manufacturing process. For example, since hair tonics often contain salicylic acid and a high percentage of alcohol, salicylic acid often is chosen as the denaturant for alcohol to be used in the manufacture of hair tonics.

Other substances sometimes employed as denaturants are pyridine, formaldehyde, aniline oil, ether, camphor, quinine, oil of wintergreen, and oil of rosemary.

Alcohol Proof.—Alcohol proof is a term frequently encountered in connection with alcohol. A solution that is 50 per cent alcohol by volume, or 42.7 per cent by weight, is termed 100 proof; thus, 95 per cent alcohol, which is as pure as can be prepared by ordinary distillation methods, is 190 proof.

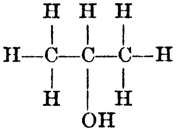
Propanol

There are two alcohols corresponding to the formula C_3H_7OH. They are known as n-propanol and isopropanol.



$$\begin{array}{ccccccccc} & & \text{H} & & \text{H} & & \text{H} & & \\ & & | & & | & & | & & \\ \text{H} & - & \text{C} & - & \text{C} & - & \text{C} & - & \text{OH} \\ & & | & & | & & | & & \\ & & \text{H} & & \text{H} & & \text{H} & & \end{array}$$

n-Propanol
B.P. 97.8° C.

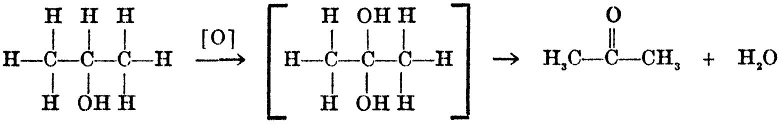


$$\begin{array}{ccccccccc} & & \text{H} & & \text{H} & & \text{H} & & \\ & & | & & | & & | & & \\ \text{H} & - & \text{C} & - & \text{C} & - & \text{C} & - & \text{H} \\ & & | & & | & & | & & \\ & & \text{H} & & | & & \text{H} & & \\ & & & & \text{OH} & & & & \end{array}$$

Isopropanol
B.P. 82.3° C.

The two compounds differ from each other in the position of the hydroxyl group. This is another example of *position isomerism.*

The reactions of n-propyl alcohol are similar to those of ethyl alcohol. Isopropyl alcohol, however, on mild oxidation yields a ketone instead of an aldehyde. Both aldehydes and ketones will be considered in more detail later.

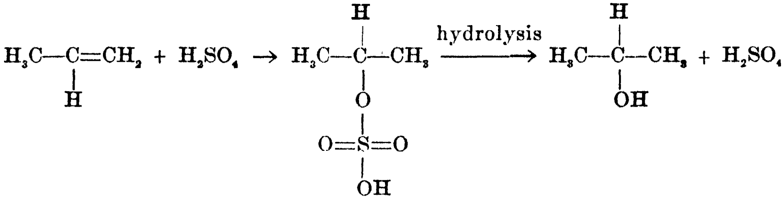


$$\begin{array}{ccccccc} & \text{H} & & \text{H} & & \text{H} & \\ & | & & | & & | & \\ \text{H}- & \text{C} & - & \text{C} & - & \text{C} & -\text{H} \\ & | & & | & & | & \\ & \text{H} & & \text{OH} & & \text{H} & \end{array} \xrightarrow{[\text{O}]} \left[\begin{array}{ccccccc} & \text{H} & & \text{OH} & & \text{H} & \\ & | & & | & & | & \\ \text{H}- & \text{C} & - & \text{C} & - & \text{C} & -\text{H} \\ & | & & | & & | & \\ & \text{H} & & \text{OH} & & \text{H} & \end{array}\right] \rightarrow \text{H}_3\text{C}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{CH}_3 + \text{H}_2\text{O}$$

Isopropyl alcohol   An intermediate product   Acetone

Normal propyl alcohol can be obtained by the fractional distillation of fusel oil. Fusel oil is a mixture of high molecular weight alcohols obtained as by-products in the manufacture of ethyl alcohol by the fermentation process.

Isopropyl alcohol is prepared from propylene, a product of petroleum cracking. Propylene is treated with concentrated sulfuric acid to form isopropyl hydrogen sulfate, which then is treated with water to give the desired alcohol.



$$H_3C{-}\underset{\displaystyle H}{C}{=}CH_2 + H_2SO_4 \rightarrow H_3C{-}\overset{\displaystyle H}{\underset{\displaystyle O{-}\overset{}{S}(=O)_2{-}OH}{C}}{-}CH_3 \xrightarrow{\text{hydrolysis}} H_3C{-}\overset{\displaystyle H}{\underset{\displaystyle OH}{C}}{-}CH_3 + H_2SO_4$$

Propylene Isopropyl hydrogen sulfate Isopropyl alcohol

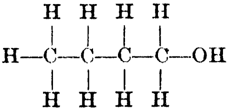
The propyl alcohols are used in antifreeze compounds, in the manufacture of esters and other derivatives, and as solvents in the lacquer and varnish industries.

Butanol

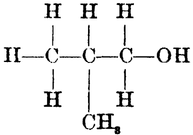
Butanol, or n-butyl alcohol, is formed by fermenting ground corn mash with the bacterium, *Clostridium acetobutylicum.* The process produces 60 per cent butanol, 30 per cent acetone, and 10 per cent ethanol. These are separated by fractional distillation. The history of the industrial production of butanol is interesting. The process was developed during World War I because of the need of acetone in the manufacture of cordite, the British type of smokeless powder. At that time no use could be found for the butanol, and since it was toxic for fish, it could not be dumped into the streams. The result was that large stores of butanol accumulated. After the war chemists turned their attention to finding a use for it. They found that the alcohol and its reaction product with acetic acid, butyl acetate, were excellent solvents for the nitrocellulose used in automobile lacquers.

At that time one problem in the mass production of automobiles was the one to two days required for the paints and varnishes to dry. Even after research had shown that automobile finishes made from a solution of nitrocellulose and butyl alcohol dried quickly and were practical, the conservativeness of the industry retarded the adoption of these types of paint. The story is told that one automobile manufacturer who had rejected the process was invited to a luncheon. While he was eating, his car was whisked away and refinished with cellulose lacquer applied with a pressure spray. When the man saw his car a short time later, his sales resistance to the new method broke down. The use of butanol-cellulose nitrate lacquers increased so rapidly that soon there was a shortage rather than a surplus of butyl alcohol.

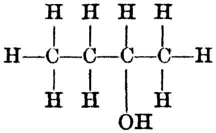
There are four alcohols corresponding to the formula, C_4H_9OH. In other words, this alcohol has four isomeric forms.



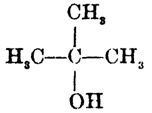
n-Butyl alcohol
(1-butanol)



Isobutyl alcohol
(2-methyl-1-propanol)



Secondary butyl alcohol
(2-butanol)



Tertiary butyl alcohol
(2-methyl-2-propanol)

The butyl alcohols have the common names shown under their structural formulas, but this method of naming the compounds is inadequate for naming the numerous isomers of the higher alcohols. By using the International system, however, it is possible logically and clearly to name all the isomers of any alcohol regardless of the number of carbon atoms. The I.U.C. ending for alcohols is *ol*, as was mentioned earlier. The carbon chain is numbered from the end nearest the hydroxyl group, that is, the position of the hydroxyl group is indicated by the smallest possible number. The position of any alkyl side chains is shown by a number, as in the case of the hydrocarbons, but the number is dependent on the location of the hydroxyl group.

The I.U.C. names of the butyl alcohols shown under the common names illustrate this system of nomenclature.

In another method of naming, the alcohols are considered as derivatives of CH_3OH, which is called *carbinol,* or less frequently, methanol. The carbon atom to which the OH group is attached is designated as the carbinol carbon atom and the groups attached to it are named. The naming of the isomeric butyl alcohols whose structural formulas have been given will illustrate the operation of the system. n-Butyl alcohol would be named n-propyl-carbinol, isobutyl would be isopropyl-carbinol, secondary butyl alcohol would become ethyl-methyl-carbinol, and tertiary butyl alcohol would be designated as trimethyl-carbinol.

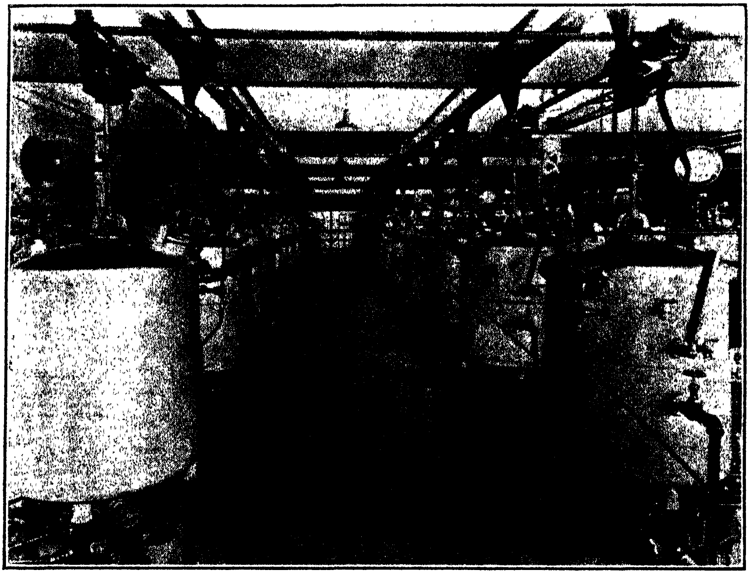
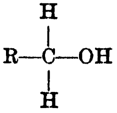


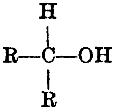
Fig. 24.—One step in the production of butyl alcohol by fermentation. The illustration shows rows of 80 gallon culture tanks for the propagation of the bacteria that convert cornstarch into such solvents as butyl alcohol, ethyl alcohol, and acetone, and the gases, carbon dioxide and hydrogen. (Courtesy of the Commercial Solvents Corporation.)

The four isomeric butyl alcohols also can be used to illustrate a method of classifying alcohols according to their structure.

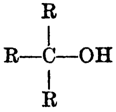
Using R to represent an alkyl group, the type formulas for the three types of alcohol are:


$$R—\overset{H}{\underset{H}{C}}—OH$$

Primary alcohol


$$R—\overset{H}{\underset{R}{C}}—OH$$

Secondary alcohol

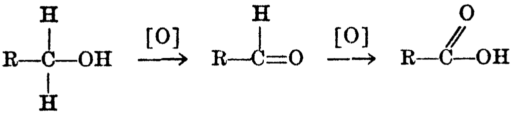

$$R—\overset{R}{\underset{R}{C}}—OH$$

Tertiary alcohol

Among the isomeric butyl alcohols, 1-butanol and 2-methyl-1-propanol are examples of primary alcohols; 2-butanol is a secondary alcohol. The fourth isomeric form, 2-methyl-2-propanol, is a tertiary alcohol.

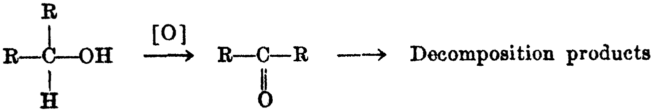
The student will find it helpful in recalling the type formulas for the three classes of alcohols if he remembers that primary alcohols have *one* R group attached to the carbon carrying the hydroxyl, secondary alcohols have *two* R groups attached to this carbon, while tertiary alcohols have *three* R groups attached to the carbon carrying the hydroxyl group. A shorthand method that sometimes is encountered for representing the three classes of alcohols is the use of I° for primary, II° for secondary, and III° for tertiary alcohols.

The importance of classifying alcohols by this method must be emphasized, for the alcohols of each class differ markedly from each other in the compounds they yield on oxidation. When *primary alcohols* are oxidized, they are converted first to *aldehydes,* and on further oxidation give *acids* containing the *same number of carbon atoms as the original alcohol.*


$$R—\overset{H}{\underset{H}{C}}—OH \xrightarrow{[O]} R—\overset{H}{C}{=}O \xrightarrow{[O]} R—\overset{O}{\overset{\|}{C}}—OH$$

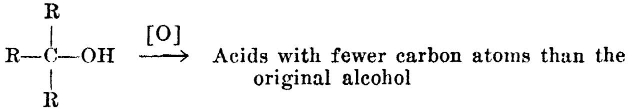
Primary alcohol Aldehyde Acid

When *secondary alcohols* are oxidized, they yield *ketones,* which are relatively stable to further oxidation.


$$R—\overset{R}{\underset{H}{C}}—OH \xrightarrow{[O]} R—\underset{O}{\underset{\|}{C}}—R \longrightarrow \text{Decomposition products}$$

Secondary alcohol **Ketone**

In the oxidation of *tertiary alcohols, the carbon chain breaks to give acids containing fewer carbon atoms than the original alcohol.*



$$R-\overset{\overset{\large R}{|}}{\underset{\underset{\large R}{|}}{C}}-OH \xrightarrow{[O]} \text{Acids with fewer carbon atoms than the original alcohol}$$

The production of butyl alcohol in the United States in 1940 was over 164,000,000 pounds, of which 100,000,000 pounds were the normal form.

Like the propyl alcohols, the butyl alcohols and their esters are used widely as solvents for "Duco" and other lacquers. One process of pulping wood for the production of paper pulp employs butyl alcohol.

Pentanol

The five-carbon alcohols, $C_5H_{11}OH$, commonly are referred to as amyl alcohols rather than as pentyl alcohols or pentanols. There are eight isomeric amyl alcohols, six of which are now of commercial importance. In order to familiarize himself with the systematic naming of the alcohols, the student should write the graphic formulas for the isomeric pentanols, and name them according to the I.U.C. system. There are four primary amyl alcohols, three secondary, and one tertiary.

Commercially, the amyl alcohols are manufactured from cracked hydrocarbons, fusel oil, and natural gas gasoline.

The principal use of the amyl alcohols is for the manufacture of amyl acetates, which result from the reaction of these alcohols and acetic acid. The amyl acetates, as well as the butyl acetates, are employed as solvents for the nitrocellulose lacquers.

Higher Alcohols

Some of the monohydroxy alcohols containing more than five carbon atoms are of commercial importance. Sodium salts of the sulfated alcohols having from 8 to 18 carbon atoms are being used in the newer types of detergent, such as Dreft and

Drene. Their general formula is $ROSO_3Na$. They lather copiously even in cold, hard water. Lauryl alcohol, $C_{12}H_{25}OH$, found in coconut oil, is one of the alcohols used for this purpose.

For the straight-chain isomers the boiling points and the specific gravities of the alcohols increase with an increase in molecular weight. Beginning with butyl alcohol, which is soluble in water only to the extent of about 8 per cent, the higher alcohols become progressively less soluble in water with an increase in the number of carbon atoms in the molecule. The higher molecular weight alcohols (above C_{12}) are solids at ordinary temperatures.

Thiols or Mercaptans

Several classes of organic compounds can be considered as cases in which a sulfur atom has replaced an oxygen atom in the molecule. The sulfur analogs of the alcohols are known as mercaptans, thiols, or thioalcohols. Their general formula is RSH. It is important to remember that the characteristic group of this class of compounds is known as the *sulfhydryl* group (—SH).

The IUC system of nomenclature uses the ending, thiol, but the name mercaptan probably is more widely used.

A general method for the preparation of thiols is analogous to the method used for the preparation of alcohols. An alkyl halide is added to a solution of potassium hydrogen sulfide, and the mixture is heated.

$$\underset{\substack{\text{Ethyl}\\\text{iodide}}}{C_2H_5I} + KSH \rightarrow \underset{\substack{\text{Ethyl metcaptan}\\\text{(ethanethiol)}}}{C_2H_5SH} + KI$$

Ethyl mercaptan is a colorless liquid insoluble in water but soluble in alcohol and possessing a most unpleasant odor. The mercaptans are notorious for bad odors. The scent of the skunk is due to butyl mercaptan. Because of the powerful odor of the lower molecular weight mercaptans, they are used as warning agents in commercial gas lines. A small amount of the mercaptan is added to the gas at the distribution station, and if a leak develops, that fact is soon known.

One of the most important reactions of the thiols is their ease of oxidation to form disulfides (dithiols).

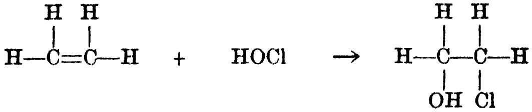
$$\underset{\text{A mercaptan}}{2\ \mathrm{RSH}} + (0) \rightarrow \underset{\substack{\text{A disulfide}\\ \text{(dithiol)}}}{\mathrm{R{-}S{-}S{-}R}} + \mathrm{H_2O}$$

Mild oxidizing agents, such as the oxygen of the air or hydrogen peroxide, will cause this reaction. The reverse reaction of reduction also takes place easily. The ease with which this oxidation-reduction reaction takes place in the human body is of great importance, especially in the case of glutathione (page 561).

Polyhydric Alcohols

Thus far our discussion has dealt with alcohols containing only one hydroxyl group in the molecule; the alcohols containing more than one such group are referred to as polyhydric or polyatomic. Since two hydroxyl groups on the same carbon form an unstable configuration, which ordinarily exists only momentarily, the simplest member of the polyhydric alcohols is a two-carbon alcohol with an hydroxyl group on each carbon atom. The dihydroxyl alcohols are called *glycols.*

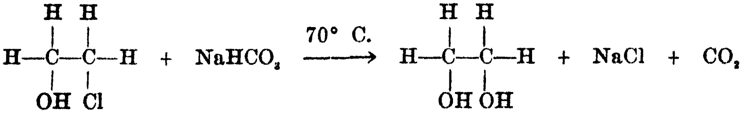
Ethylene Glycol.—The simplest glycol bears the name ethylene glycol, or simply glycol. Commercially it is prepared from ethylene. The ethylene first is reacted with hypochlorous acid to give ethylene chlorohydrin.



$$\mathrm{H{-}\overset{H}{C}{=}\overset{H}{C}{-}H} + \mathrm{HOCl} \rightarrow \mathrm{H{-}\underset{OH}{\overset{H}{C}}{-}\underset{Cl}{\overset{H}{C}}{-}H}$$

Ethylene Hypochlorous acid Ethylene chlorohydrin

Ethylene chlorohydrin then is hydrolyzed to give glycol.



$$\mathrm{H{-}\underset{OH}{\overset{H}{C}}{-}\underset{Cl}{\overset{H}{C}}{-}H} + \mathrm{NaHCO_3} \xrightarrow{70°\ \mathrm{C.}} \mathrm{H{-}\underset{OH}{\overset{H}{C}}{-}\underset{OH}{\overset{H}{C}}{-}H} + \mathrm{NaCl} + \mathrm{CO_2}$$

Ethylene chlorohydrin Sodium bicarbonate Ethylene glycol

Glycol is derived from a Greek word *glykys,* meaning sweet. The compound is a sweet, syrupy, clear liquid. It reacts much as do the other alcohols, differing in that it has two reactive hydroxyl groups.

Ethylene glycol forms a dinitrate with nitric acid. This compound is added to dynamite to lower the freezing point. Ordinary dynamite freezes easily, and most of the accidents in handling the compound formerly were the result of attempts to thaw the frozen explosive. However, if solutions of glycol dinitrate are added, the freezing point can be lowered to as much as –8.7° F. Glycol dinitrate is itself an explosive so that its addition to dynamite does not detract from the effectiveness of the latter.

Ethylene glycol is ideally suited for use as an antifreeze in automobile radiators. The boiling point of the compound is 197.5° C., and at the ordinary operating temperatures of the engine it does not have an appreciable vapor pressure. This means that the tendency to evaporate is small. Ethylene glycol mixes with water in all proportions and is noncorrosive. The commercial antifreeze compounds, ''Prestone'' and ''Zerone,'' are mainly ethylene glycol with a small amount of other material added to prevent the formation of rust by the water present in the radiator. An aqueous mixture of 60 per cent ethylene glycol freezes at –40° F.

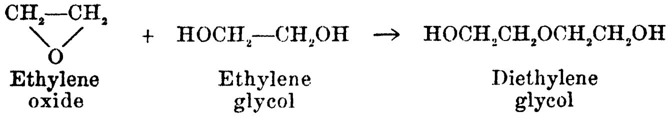
Hectograph stencils are made by pouring a hot glycol-gelatin-glue solution into a pan and allowing it to set. Hectographing affords a simple, inexpensive substitute for printing or mimeographing, and now is used in many offices and schools.

Ethylene glycol is used in hydraulic brake fluid. It also is used as a cooling agent for airplane motors. For this use it has the advantage that the engine can be operated at a high temperature without loss of the coolant. Since airplane radiators need not be of large capacity, they can have a small frontal area with the consequent advantage of less wind resistance; this also makes possible a smaller engine weight. The use of ethylene glycol as a high temperature cooling agent has been extended to x-ray tubes, machine guns, and army tanks.

Solutions of boric acid and ethylene glycol are used in the compact "jelly-roll" type of electrolytic condenser. These condensers are formed of alternate layers of aluminum foil separated by paper or cloth, which has been impregnated with the glycol-boric acid mixture. The nonconductor of the condenser is a film of aluminum oxide deposited on one sheet of the aluminum foil. Ethylene glycol is well adapted for use in such condensers because it is nonvolatile and does not corrode aluminum. Without this compact type of condenser it is doubtful whether the midget radio sets would have been possible.

Ethylene glycol and glycerol seem to be about equal in producing the desired resiliency in the glue-type rollers used for printing presses.

Diethylene Glycol, $HOCH_2CH_2OCH_2CH_2OH$.—When ethylene glycol is heated with ethylene oxide, diethylene glycol results.



Diethylene glycol is used as a lubricant in the textile industry. In the preparation of wool for spinning the fibers must be scoured to remove dirt. This process also removes most of the natural oils, and the fibers tend to become slightly brittle. It is necessary, therefore, to coat them with a product that will permit one fiber to pass easily over the other in the mechanical operations involved in the processing of the fibers into yarn. Diethylene glycol has been found very suitable for this purpose.

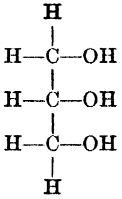
The compound is added to the starch solutions used for sizing textiles. It prevents the starch sizing on the fibers from drying out and flaking off.

Because of its chemical structure, diethylene glycol has proved to be an excellent solvent for the dyes used on textiles.

Diethylene glycol is toxic. If this property had been known generally before 1937, probably the death of nearly a hundred persons who died from taking elixir of sulfanilamide would have been prevented. The solvent in the elixir was diethylene glycol.

As we shall see later (page 469), the discovery of sulfanilamide and its derivatives probably was one of the most sensational developments in medicine within the last twenty-five years. The responsibility for the deaths caused by the ingestion of the elixir, therefore, was fixed on the diethylene glycol. Fortunately, a new pure food and drug act prevents the sale of new remedies until they have been tested fully on experimental animals and on human patients.

Glycerol, $C_3H_5(OH)_3$.—The simplest trihydroxy alcohol is known as glycerin or glycerol. Its graphic formula shows that it contains two primary and one secondary alcoholic groups.

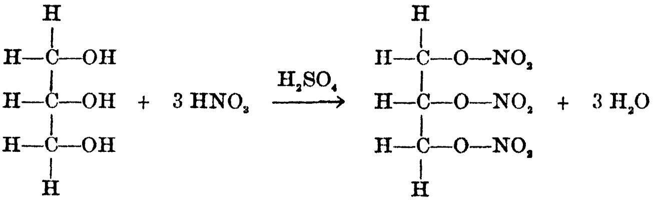


Large quantities are obtained as a by-product of the soap industry. Fats contain glycerol as a part of the molecule. The glycerol is set free when the fats are hydrolyzed with alkalies to form soaps.

A recent development is the manufacture of glycerol by the chlorination of propylene at 400° to 600° C., forming allyl chloride, $CH_2{=}CH{—}CH_2Cl$. This compound is converted to glycerin dichlorohydrin, which then is hydrolyzed to glycerol. Large quantities of glycerol potentially are available from the petroleum industry. It seems likely that this situation will stabilize the price of glycerol, which has fluctuated widely in the past, since it depends on the amount produced by the soap industry.

Like glycol, glycerol is a clear, syrupy, sweet-tasting liquid that is miscible in all proportions with water and with alcohol. It is hygroscopic, and, therefore, absorbs moisture from the air.

In general, its chemical properties are similar to those of the other alcohols. Its most important chemical reaction is with nitric acid to yield glyceryl trinitrate, commonly known as nitroglycerin. Glycerol is treated with concentrated nitric acid in the presence of sulfuric acid, which acts as a dehydrating agent. The reaction mixture is kept below room temperature.



$$\begin{array}{c} \mathrm{H} \\ | \\ \mathrm{H-C-OH} \\ | \\ \mathrm{H-C-OH} \\ | \\ \mathrm{H-C-OH} \\ | \\ \mathrm{H} \end{array} + 3\,HNO_3 \xrightarrow{H_2SO_4} \begin{array}{c} \mathrm{H} \\ | \\ \mathrm{H-C-O-NO_2} \\ | \\ \mathrm{H-C-O-NO_2} \\ | \\ \mathrm{H-C-O-NO_2} \\ | \\ \mathrm{H} \end{array} + 3\,H_2O$$

Glycerol Nitric acid Glyceryl trinitrate

The nitroglycerin formed is a liquid, insoluble in water and very sensitive to shock. The basis for the effectiveness of nitroglycerin as an explosive lies in the fact that all the products of the explosive reaction are gases. Furthermore, the heat of the reaction causes a considerable increase in the volume of the gases. At the time of the explosion the gases formed occupy 10,000 times the volume of the liquid material.

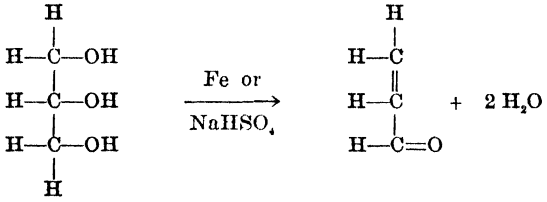
$$\underset{\text{Nitroglycerin}}{4\,C_3H_5(NO_3)_3} \rightarrow 12\,CO_2 + 10\,H_2O + 6\,N_2 + O_2 + \text{heat}$$

Liquid nitroglycerin in long cans is used in "shooting" oil wells. The violent explosion breaks the oil-retaining sandstone, and often turns a nonproducing well into a flowing one.

Since nitroglycerin explodes so readily with a slight jar or shock, the liquid is dangerous to handle or transport. This difficulty was overcome by Alfred Nobel, a Swedish engineer and founder of the Nobel Peace Prizes. He found that by mixing the nitroglycerin with infusorial earth, "kieselguhr," the substance was safe to handle and did not lose any of its explosive power. Such a mixture he called dynamite. Nitroglycerin in the form of dynamite requires a detonator to explode it. In practice, the detonator present in dynamite caps is mercuric fulminate, $Hg(ONC)_2$.

Glyceryl trinitrate is employed in medicine to dilate the blood vessels in certain heart conditions and to secure relief from pain in such conditions as angina pectoris and gall bladder colic.

A reaction peculiar to glycerol is its dehydration by heating to form acrolein, especially in the presence of metals or sodium bisulfate. This compound is an aldehyde with a pungent, disagreeable odor. Acrolein is responsible for the acrid odor of overheated bacon and other fat-containing substances.



$$\begin{array}{c}\mathrm{H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H}\end{array} \xrightarrow[\mathrm{NaHSO_4}]{\text{Fe or}} \begin{array}{c}\mathrm{H}\\ |\\ \mathrm{H{-}C}\\ \|\\ \mathrm{H{-}C}\\ |\\ \mathrm{H{-}C{=}O}\end{array} + 2\,\mathrm{H_2O}$$

Glycerol Acrolein

Acrolein sometimes is used as a warning agent in refrigerator gases, and in the gases used for domestic heating and cooking purposes. Because of the pungent smell of acrolein, there is no difficulty in detecting escaping gas.

Glycerol has many uses other than its use in the manufacture of explosives. *Ester gums,* for example, are prepared by heating rosin and glycerin under pressure until condensation takes place. They are of primary importance in the manufacture of enamels, paints, and cellulose lacquers, and when they are combined with tung oil, they form waterproof varnishes. The reaction between glycerol and phthalic anhydride as well as glycerol and maleric anhydrides yields *alkyd resins.* In 1946 over 188 million pounds of these resins were used in lacquers, enamels, and other protective coatings.

The hygroscopic property of glycerol is utilized in the application of medicine to the skin and mucous membranes. The effect of pure (100 per cent) glycerol mixed with healing substances is to produce mild irritation by the withdrawal of water. Thus the penetration of the healing ingredients is facilitated.

When glycerol is diluted about 50 per cent with water, it loses its irritating effects and acts as an emollient and demulcent. Due to this property it is an important ingredient in nearly all hand lotions and ointments.

Dilute solutions of glycerol are excellent solvents for a variety of substances used in the field of medicine. The sweet taste of the compound is an advantage in making many medicines more palatable. In cough syrups glycerol not only soothes the mucous membranes, but also makes the liquid more agreeable to take.

The glyceryl phosphates of calcium, iron, and sodium are ingredients of many popular "nerve tonics." These are probably worthless.

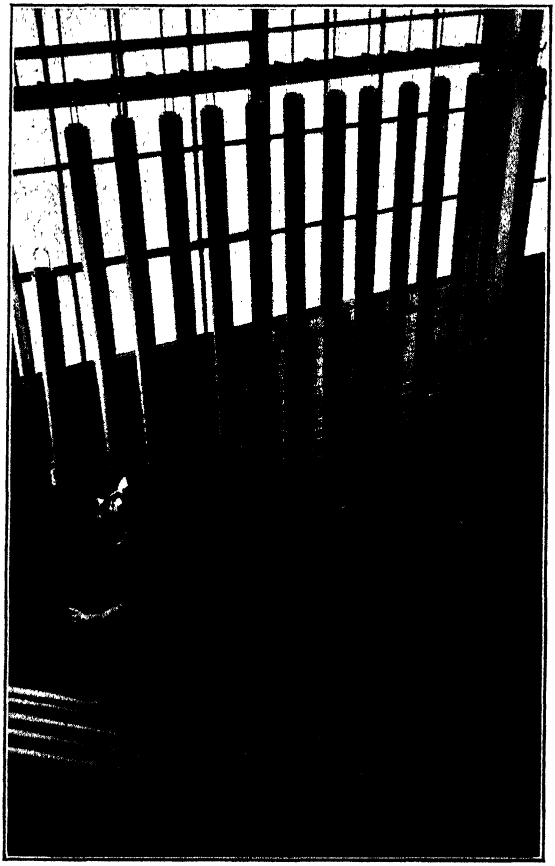


Fig. 25.—Nitroglycerin in long, laminated Bakelite shells used for shooting oil wells. The force of the explosion breaks the oil-retaining sandstone thus releasing the oil. The shells made of Bakelite shatter into small particles, thereby minimizing danger to workers and drilling equipment. (Courtesy of the Bakelite Corporation, New York, N. Y.)

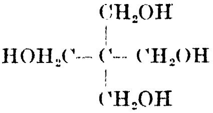
Glycerol can be taken internally in fairly large quantities without harmful effects. This is to be expected, since the hydrolysis of fats by enzymes in the intestine splits fatty foods to glycerol and fatty acids during digestion.

A mixture of glycerol and litharge is used by plumbers to form a strong, waterproof cement.

If glycerol is used to moisten the fingers, the separating and handling of sheets of paper is done easily without resorting to the familiar, unsanitary method. This use of glycerol is a common practice among printers and mimeographers.

The hygroscopic property of glycerol is a basis for its use in printing inks, stamp pads, and hectograph sheets.

Pentaerythritol.—A polyhydroxy compound, pentaerythritol, is finding application in coating compositions of alkyd, urea, formaldehyde, and modified phenolic resins; and in plasticizers, emulsifying agents, and waxes.



$$\begin{array}{c} CH_2OH \\ | \\ HOH_2C-C-CH_2OH \\ | \\ CH_2OH \end{array}$$

Pentaerythritol

Study Questions

1. A certain substance has the following percentage composition: carbon 65.0 per cent, hydrogen 13.5 per cent, and oxygen 21.5 per cent. A liter of the vapor of this substance weighs 2.42 g. at 100° C. and 760 mm. What is its molecular formula?
2. Describe the process for the preparation of methyl alcohol by the distillation of hard wood.
3. How can methanol be prepared from coke?
4. Why is it dangerous to use methyl alcohol as an antifreeze for automobile radiators?
5. How is ethyl alcohol prepared commercially? What are several other names for this compound?
6. Why is it impossible to obtain 100 per cent ethyl alcohol by a process of fractional distillation?
7. List four not too closely related uses of ethyl alcohol.
8. What is meant by denatured alcohol? Why is alcohol denatured?
9. If an alcohol is 160 proof, what percentage of alcohol by volume does it contain?
10. In what respects do propyl alcohol and isopropyl alcohol differ from each other?
11. What is an outstanding industrial use for butyl alcohol?

12. Write the structural formulas for the isomeric amyl alcohols. Classify them as to whether they are primary, secondary, or tertiary alcohols.
13. How do primary, secondary, and tertiary alcohols differ from each other chemically?
14. What is the generic name given to the dihydroxy alcohols? What is the simplest member of this class, and for what is it used?
15. Write the equation for the formation of the trinitro substitution product of glycerol.
16. How is dynamite made?
17. How do you account for the fact that burning bacon gives off an odor of acrolein?
18. Formerly the price of glycerol was dependent on the amount of the material produced as a by-product of the soap industry. Now this is no longer true. Why?

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CHAPTER VII

ETHERS

The class of organic compounds known as ethers contain two alkyl radicals attached to an oxygen atom. The type formula for an ether is R—O—R′, in which R and R′ can be either the same or different alkyl radicals, thus making possible the existence of either simple or mixed ethers.

Methyl Ether, CH_3—O—CH_3.—Methyl ether (dimethyl ether) is the simplest ether. It can be prepared by the action of sulfuric acid on methyl alcohol. The chief use of methyl ether is as a refrigerant. It is well adapted to this use since it can be allowed to come in direct contact with foodstuffs during "quick freezing" processes without imparting undesirable tastes or odors to the products. When foods are frozen quickly, the ice crystals formed are usually too small to rupture the cell walls, thus helping to preserve the natural flavor and appearance of the foods when they subsequently are thawed.

Ethyl Ether, C_2H_5—O—C_2H_5.—Ethyl ether (diethyl ether) is by far the most important representative of the aliphatic ethers. It is the compound meant when the unqualified term ether is used. It is prepared both commercially and in the laboratory by heating ethyl alcohol with sulfuric acid at 140° C. The reaction proceeds in two stages. First, ethyl hydrogen sulfate and water are formed.

$$\underset{\text{Ethyl alcohol}}{C_2H_5OH} + \underset{\text{Sulfuric acid}}{H_2SO_4} \rightarrow \underset{\substack{\text{Ethyl hydrogen}\\ \text{sulfate}}}{C_2H_5OSO_3H} + H_2O$$

On further heating in the presence of an excess of alcohol the ethyl hydrogen sulfate reacts with a molecule of alcohol to form ether and regenerate the sulfuric acid.

$$\underset{\substack{\text{Ethyl hydrogen}\\ \text{sulfate}}}{C_2H_5}\boxed{OSO_3H \;+\; \underset{\substack{\text{Ethyl}\\ \text{alcohol}}}{H}}OC_2H_5 \xrightarrow{130°\text{-}140°\ C.} \underset{\substack{\text{Diethyl}\\ \text{ether}}}{C_2H_5\text{—}O\text{—}C_2H_5} + \underset{\substack{\text{Sulfuric}\\ \text{acid}}}{H_2SO_4}$$

From the equations it would appear that, as the acid is regenerated, a given amount of sulfuric acid would convert an unlimited amount of alcohol to ether. In practice, this is found not to be true. The sulfuric acid gradually is diluted by the water formed during the reaction. Side reactions that take place to a small extent also consume some of the sulfuric acid. For these reasons, it is necessary to add more sulfuric acid at intervals, although a given amount of acid has been known to form a quantity of ether equivalent to 250 times its weight.

A more general method of preparing ethers, devised as early as 1851, is known as the Williamson synthesis. In this method an alkyl halide reacts with an alkoxide or a sodium alcoholate to form either a simple or a mixed ether, depending on the reactants used.

$$\underset{\substack{\text{Ethyl}\\ \text{iodide}}}{C_2H_5I} + \underset{\substack{\text{Sodium}\\ \text{ethylate}}}{NaOC_2H_5} \rightarrow \underset{\substack{\text{Ethyl ether}\\ \text{(a simple ether)}}}{C_2H_5{-}O{-}C_2H_5} + NaI$$

or

$$\underset{\substack{\text{Methyl}\\ \text{iodide}}}{CH_3I} + \underset{\substack{\text{Sodium}\\ \text{propylate}}}{NaOC_3H_7} \rightarrow \underset{\substack{\text{Methyl propyl ether}\\ \text{(a mixed ether)}}}{CH_3{-}O{-}C_3H_7} + NaI$$

Diethyl ether is a water-clear liquid that is lighter than water and is soluble in water only to the extent of about 8 per cent. A physical property of ether that should be remembered is that it boils at 35° C. (95° F.). Accordingly, even at ordinary room temperatures (20° to 25° C.) ether in an open vessel will evaporate rapidly. Because ether vapors are very inflammable, every precaution should be observed in using ether so as to prevent dangerous fires. It is a good policy not to permit a free flame in the same room where ether is being used, for a draft of air might carry the ether fumes to the flame and cause a fire to strike back to the ether container. In addition to the inflammability of ether vapor, mixtures of it with air, ranging in concentration from 1 to 51 per cent, are explosive.

The most characteristic and important chemical property of ethyl ether, and, indeed, of ethers in general, is their inertness and nonreactivity. This is the reason that ethyl ether is so valuable and so widely used as a solvent for organic substances.

Since the majority of organic substances are more soluble in ether than in water, and since ether is so slightly soluble in water, it is useful for extracting organic substances from aqueous solutions. The organic substance, being more soluble in the ether, will concentrate in the upper, lighter ether layer, which can be separated from the aqueous layer by means of a separatory funnel.

In the laboratory, the solvent power of ether is utilized in the quantitative extraction of fats and oils.

Although ethers are inert to most substances, hydrogen iodide will react with them in the cold to give two molecules of alkyl halide and water. The first products of the reaction are a molecule of alkyl halide and a molecule of alcohol; the latter, on further action of the hydrogen iodide, also is converted to an alkyl halide.

$$\underset{\substack{\text{Diethyl}\\\text{ether}}}{C_2H_5{-}O{-}C_2H_5} + \underset{\substack{\text{Hydrogen}\\\text{iodide}}}{HI} \rightarrow \underset{\substack{\text{Ethyl}\\\text{iodide}}}{C_2H_5I} + \underset{\substack{\text{Ethyl}\\\text{alcohol}}}{C_2H_5OH} \xrightarrow{HI} \underset{\substack{\text{Ethyl}\\\text{iodide}}}{2\,C_2H_5I} + H_2O$$

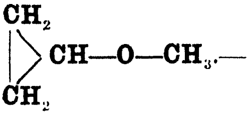
Ethers are soluble in cold sulfuric acid. If water is added to such a solution, the ether can be recovered unchanged, but if the solution is heated, ethyl sulfuric acid and water are formed.

When ether is exposed to the air, small quantities of peroxides are formed. These render ether both toxic and explosive. The peroxides are less volatile than the ether itself; thus, when ether containing peroxides is distilled, the peroxides concentrate in the distillation flask, and in some cases, may be an explosion hazard. The formation of peroxides can be retarded or prevented by storing ether in copper-lined containers, or, in the case of anhydrous ether, by the addition of metallic sodium wire. Ethers containing peroxides are unfit for anesthetic use; hence, ether used for anesthetic purposes must be carefully purified.

Ether is still probably the most frequently used general anesthetic. It appears likely that the use of ether for this purpose was made independently by Dr. Long of Georgia in 1842, by Dr. Morton, a Boston dentist, in 1846, and by Dr. Simpson of Edinburgh in 1848.

Diethyl ether in some respects is an ideal anesthetic. It is easy to administer; it causes excellent muscular relaxation; there is less danger of an overdose than with most other anesthetics; and it does not alter the pulse rate, the rate of respiration, or the blood pressure very much. It has certain disadvantages, however, which explains its gradual decline in popularity in recent years: (1) It is irritating to the mucous membrane of the respiratory passages; (2) there is some danger of postoperative pneumonia; (3) nausea is a usual postoperative symptom; (4) it causes the accumulation of harmful acids in the blood if administered over a long period of time; and (5) there is some slight damage to the liver and kidneys. However, ether is preferred to chloroform as an anesthetic because it has fewer undesirable effects.

Divinyl ether ($CH_2{=}CH{-}O{-}CH{=}CH_2$) also is used as an anesthetic. Like diethyl ether, it can be administered by dropping some of it on a gauze cone or a piece of gauze held over the patient's nose and mouth. It works more quickly than regular ether, producing anesthesia in 0.5 to 1.5 minutes. Recovery, also, is more rapid than from regular ether. Both diethyl ether and divinyl ether are highly volatile liquids and form explosive mixtures with air so that flames or sparks must be carefully avoided in the operating room.

Cyclopropylmethyl Ether,  —This ether, which might be considered as a hybrid of cyclopropane and methyl ether, shows considerable promise as an anesthetic. At present, however, it is not widely available.

Isopropyl Ether, $(CH_3)_2CH{-}O{-}HC(CH_3)_2$. — Isopropyl ether has a boiling point of 69° C. It is prepared commercially from propylene, which is one of the unsaturated hydrocarbons in the gases from the cracking process. As is true of ethyl ether, the principal use of this compound is as a solvent. It is used in the solvent extraction method for the separation of acetic acid and lactic acid from their dilute aqueous solutions. Considerable quantities of isopropyl ether are being blended with gasoline to obtain special antiknock fuels for airplanes.

Dichlorodiethyl Ether, $\mathbf{ClCH_2CH_2{-}O{-}CH_2CH_2Cl}$.—A compound that can be considered as a derivative of ethyl ether, although it is not prepared directly from it, is dichlorodiethyl ether. Ethylene chlorohydrin is treated with concentrated sulfuric acid at 100° C. to give this compound.

$$\underset{\text{Ethylene chlorohydrin}}{\mathrm{ClCH_2CH_2}\boxed{\mathrm{OH\ +\ H}}\mathrm{OCH_2CH_2Cl}} \xrightarrow[100^\circ\ \mathrm{C.}]{\mathrm{H_2SO_4}} \underset{\text{Dichlorodiethyl ether}}{\mathrm{ClCH_2CH_2{-}O{-}CH_2CH_2Cl}} + \mathrm{H_2O}$$

The halogen-containing ether thus formed is a particularly good solvent for oils, fats, and waxes. Dichlorodiethyl ether, employed industrially under the trade name "Chlorex," is the chlorinated product used in an important process for the production of high-grade lubricating oils from mid-continental and other crude oils. In this process, the chlorinated ether acts as a selective solvent for waxes and asphatic compounds that are not removed by ordinary distillation methods, and that would cause sludging and other undesirable characteristics in the lubricating oils.

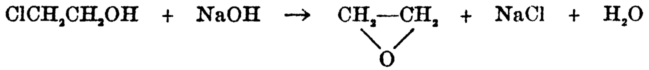
Thio Ethers.—Compounds in which the oxygen present in ordinary ethers is replaced by sulfur are known as thio ethers. Mustard gas, β,β'-dichlorodiethyl sulfide, is an example of this type of compound.

$$\underset{\text{Mustard gas}}{\mathrm{ClCH_2{-}CH_2{-}S{-}CH_2{-}CH_2Cl}}$$

This compound really is not a "gas" at all, but is an oily liquid boiling at 217° C. It was designated as a gas because very small concentrations of the material in the air over a battle area were highly effective. It is an extremely powerful vesicant (blistering agent), and has a very destructive effect on the respiratory tract. Mustard gas can be stopped from entering the lungs by a suitable gas mask, but it is difficult to prevent it from penetrating clothes, leather, and rubber.

Oxides.—The oxides are a class of compounds that contain an oxygen atom linked to carbon atoms of an alkyl group, thus resembling ethers in structure. They differ from ethers, however, in that the carbon atoms linked to the oxygen atom are in the same alkyl group. This results in the oxides having a cyclic structure.

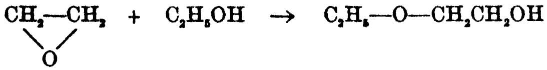
The simplest member of this group of compounds is *ethylene oxide,* which is formed by the action of *strong* alkali on ethylene chlorohydrin.



Ethylene chlorohydrin

Ethylene oxide

The boiling point of ethylene oxide is 10.7° C., so that at room temperature it is a colorless gas, very soluble in water, alcohol, and ether. Ethylene oxide differs markedly from the straight-chain ethers in that it is a very reactive compound. Most of the reactions of ethylene oxide involve the opening of the oxygen bridge, followed by addition to the valences thus set free. With alcohol, for example, the monoethyl ether of ethylene glycol is formed.



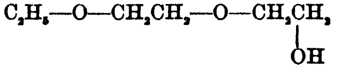
Ethylene oxide

Ethyl alcohol

Ethylene glycol monoethyl ether

The product formed bears the trade name "cellosolve" and is widely used as a solvent for the nitrocellulose lacquers, which are the principal automobile finishes. The methyl ether formed in a similar way by the reaction of methyl alcohol and ethylene oxide is known as "methyl cellosolve." Butyl alcohol, similarly, yields the ether known as "butyl cellosolve." Since all the cellosolve solvents are both alcohols and ethers, they dissolve both in water and in organic solvents. They are extensively used as solvents for lacquers and dyes, and are components of quick drying varnishes and enamels.

When ethylene oxide reacts with ethylene glycol, diethylene glycol, $HOCH_2CH_2{-}O{-}CH_2CH_2OH$, is formed. The ethers of this compound are marketed as the various "Carbitol" solvents.

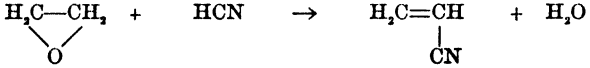


$$C_2H_5{-}O{-}CH_2CH_2{-}O{-}CH_2\underset{\substack{|\\ OH}}{C}H_2$$

Diethylene glycol monoethyl ether
(Carbitol solvent)

These are especially useful in the dyestuffs industry. They are also of value in the preparation of nonaqueous stains for wood, because they prevent "raising" in the grain of the wood.

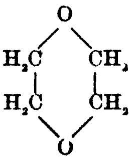
Ethylene oxide is used in the preparation of acrylonitrile. The equation for the preparation of this compound is:



Ethylene oxide
Hydrocyanic acid
Acrylonitrile

Acrylonitrile reacts with butadiene made from petroleum to give a type of synthetic rubber known as Perbunan. Ameripol, the synthetic rubber manufactured by the Goodrich Company, also involves the use of acrylonitrile.

Dioxane.—Dioxane, a cyclic ether, is a colorless liquid with a faint, pleasant odor.



Dioxane

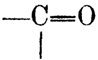
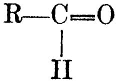
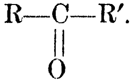
It can be prepared by the distillation of ethylene glycol with sulfuric acid. It has the interesting property of being water soluble, and in addition dissolves a wide variety of organic substances, such as oils, waxes, resins, greases, and lignin. Because of this unusual property of mixing with both water and paraffin wax, dioxane is used by histologists in mounting tissue specimens.

Study Questions

1. What is the chemical name of the common ether used for anesthetic purposes? How is this ether prepared?
2. Write formulas and names for three simple ethers and three mixed ethers.
3. What precautions should be taken in a chemical laboratory when ether is being used as a reagent and why?
4. Describe how the solvent properties of ether could be utilized to remove the fat from an aqueous mixture of ground cottonseed.
5. Why is diethyl ether a valuable anesthetic?
6. What is the role played by dichlorodiethyl ether in the production of high-grade lubricating oils?
7. How are oxides related to ethers? How do they differ from ethers?
8. Write the equation for the formation of butyl cellosolve. Why are the cellosolve products more versatile solvents than either alcohols or ethers?
9. What is dioxane and for what is it used?

CHAPTER VIII

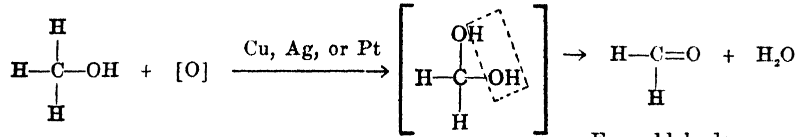
ALDEHYDES AND KETONES

Introduction.—We now come to the study of another group of compounds, which are the first oxidation products of alcohols. *Aldehydes are formed by the oxidation of primary alcohols, and ketones are formed by the oxidation of secondary alcohols.* Since both aldehydes and ketones contain the  $-\underset{|}{C}=O$ linkage, known as the *carbonyl group,* it is fitting that they be dealt with in the same chapter. Aldehydes have the type formula  $R-\underset{\underset{H}{|}}{C}=O$, R representing a carbon to carbon linkage except in the case of the first member of the homologous series of aldehydes. The type formula for ketones is  $R-\underset{\underset{O}{\|}}{C}-R'$. Both types of compound really are unsaturated, for the oxygen is combined by means of a double bond. The student is cautioned against writing the formulas for aldehydes as $R-C-OH$, since this would lead to the belief that a monovalent hydroxyl radical is attached to the carbon, whereas, in reality, a divalent oxygen and a hydrogen atom are linked separately to the carbon. However, the type formula for aldehydes is often abbreviated as $R-CHO$.

Formaldehyde, $H-CHO$.—The simplest aldehyde commonly is known as formaldehyde. However, according to the I.U.C. system of nomenclature, the compound would be called methanal. When aldehydes are named by this system, the final *e* is dropped from the paraffin hydrocarbon name, and an *al* ending is added. The common names of the aldehydes are derived from the acids they yield on oxidation. For example, formaldehyde yields formic acid, and acetaldehyde oxidizes to give acetic acid.

Formaldehyde can be prepared by the controlled oxidation of methyl alcohol. The alcohol vapor is passed over a heated catalyst, such as copper or silver gauze.

The accepted mechanism for the oxidation of alcohol will aid the student in remembering the structural formulas for aldehydes and ketones. It has been found that in the oxidation of any organic compound, further oxidation is most likely to take place at the point where some oxidation has already occurred. For example, in the oxidation of alcohols, further oxidation will take place on the carbon atom to which the hydroxyl is attached, yielding a compound containing two hydroxyl groups on the same carbon atom. With only a few exceptions, compounds with two hydroxyl groups on the same carbon atom are unstable. In the oxidation of methyl alcohol (see below) the instability of the compound with two hydroxyl groups on the same carbon is indicated by placing brackets around this compound. This method of indicating the instability of a compound should be remembered by the student whenever he encounters such a representation. When a compound is thus represented, it signifies that this compound is unstable, exists as an intermediate form, and is never isolated. In the case of the intermediate compound in the oxidation of alcohols, water separates from the two hydroxyl groups, thus forming the carbonyl group.



$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}OH} + [\mathrm{O}] \xrightarrow{\text{Cu, Ag, or Pt}} \left[\mathrm{H{-}\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}{-}OH}\right] \rightarrow \mathrm{H{-}\underset{\displaystyle H}{C}{=}O} + \mathrm{H_2O}$$

Methyl alcohol

Intermediate compound

Formaldehyde

Formaldehyde is a gas with a sharp, pungent odor. Usually it is handled either as an aqueous solution, formalin, which contains approximately 40 per cent formaldehyde, or as a solid polymer, paraformaldehyde, which liberates the gas when heated. Both forms are used as disinfectants.

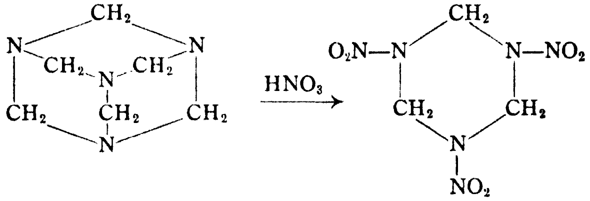
As is frequently characteristic of the first member of an homologous series, formaldehyde exhibits an anomalous chemical behavior. It undergoes a number of reactions that are not characteristic of the other aldehydes. These special reactions are:

1. **With ammonia, formaldehyde reacts to give hexamethylenetetramine, or urotropin (methenamine, hexamine).**

$$\underset{\text{Formaldehyde}}{6\,\text{H—CHO}} + 4\,\text{NH}_3 \rightleftarrows 6\,\text{H}_2\text{O} + \underset{\text{Urotropin}}{(\text{CH}_2)_6\text{N}_4}$$

This compound is used as an antiseptic for the urinary tract. Its activity is thought to be due to the liberation of formaldehyde in an acid urine. To insure that the urine will be acid, some substance such as dihydrogen phosphate often is administered with the urotropine.

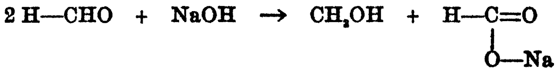
Hexamethylenetetramine is used as a source of formaldehyde in the manufacture of the Bakelite type of plastics, and for the manufacture of Cyclonite, a powerful explosive.



Hexamethylenetetramine Cyclonite (RDX)

During World War II about 360 tons per day of RDX were manufactured in the United States. Since this explosive is too sensitive to be used alone in munitions, it is "phlegmatized" by the addition of other materials. Cyclonite was the principal explosive in the "earthquake" bombs used for the destruction of submarine pens and for bombing battleships.

2. **When formaldehyde reacts with sodium hydroxide, simultaneous oxidation and reduction, or *dismutation*, takes place. Methyl alcohol is the reduction product, and formic acid, present as the salt, is the oxidation product.**



$$\underset{\text{Formaldehyde}}{2\,\text{H—CHO}} + \text{NaOH} \longrightarrow \underset{\text{Methyl alcohol}}{\text{CH}_3\text{OH}} + \underset{\text{Sodium formate}}{\text{H—}\underset{\substack{|\\ \text{O—Na}}}{\text{C}}\text{=O}}$$

Formaldehyde Methyl alcohol Sodium formate

This reaction has been named after Cannizzaro, its discoverer. It takes place most readily in the case of aldehydes that have no hydrogen on the carbon adjacent to the carbonyl group; however, under special conditions of alkalinity and with the aid of a catalyst other aldehydes can be made to undergo the same type of reaction.

3. When formalin is treated in the laboratory with saturated calcium hydroxide solution, it combines with itself to give as an end product a sweet-tasting syrup, formose, which contains a mixture of sugars. Butlerow carried out this laboratory synthesis of sugars in 1861.

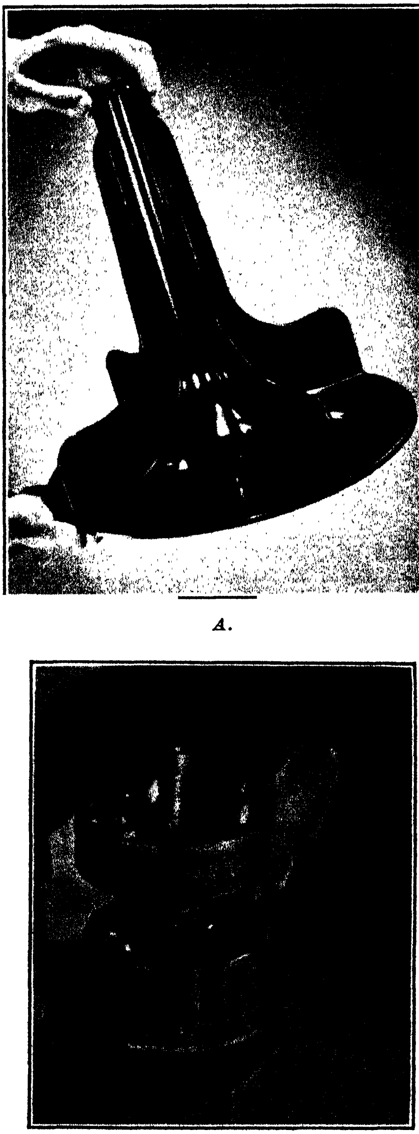
$$\underset{\text{Formaldehyde}}{6\,\text{H—CHO}} \rightarrow \underset{\text{Formose, a mixture of sugars}}{C_6H_{12}O_6}$$

This is an important type of reaction, for it is believed that this is the mechanism by which plants produce sugars. If this is the case, possibly the first step preceding the combining of formaldehyde to sugars is the formation of formaldehyde by the plants from carbon dioxide and water.

$$CO_2 + H_2O \rightarrow O_2 + \text{H—CHO}$$

4. Formaldehyde forms useful resins with some compounds. For example, with urea the product is known as ''Beetle''; with casein, ''Karolith'' is formed; when formaldehyde reacts with phenol, ''Bakelite'' is the product. Such plastics are used widely for making decorative jewelry, buttons, buckles, knobs and handles, bottle caps, fixtures for automobiles, and a wide variety of other articles. The total production of formaldehyde (37 per cent purity) in the United States increased from 180,000,000 pounds in 1940 to 458,877,000 pounds in 1946.

Uses of formaldehyde. Formaldehyde gas kills the lower forms of life, so that it can be used as a fumigant; generally, paraformaldehyde candles are burned as the source of the gas. This aldehyde hardens and prevents bacterial decomposition of proteins and so is used as an embalming agent and as a preservative for biological specimens. When viruses and bacterial toxins are treated with formaldehyde, they tend to lose their infectious properties and may in some cases become useful im-



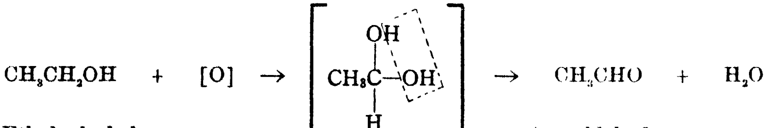
A.

B.

Fig. 26.—*A*, Washing machine agitator and, *B*, oil well drilling part molded from shock-resistant, phenol-formaldehyde type of plastic. The material is made shock resistant by the incorporation of fibrous fillers. (Courtesy of the Bakelite Corporation.)

munizing agents. The tanning of leather and the manufacturing of mirrors consume large quantities of formaldehyde. Since it is a very reactive compound, formaldehyde frequently is employed in synthetic chemistry.

Acetaldehyde, CH_3CHO.—Acetaldehyde, or ethanal, as it is called in the I.U.C. system, is the second member of the homologous series of saturated aldehydes. It is a colorless liquid of strong odor that boils at 20.2° C. It can be prepared in the laboratory by the careful oxidation of ethyl alcohol, using sodium dichromate and sulfuric acid as oxidizing agents.

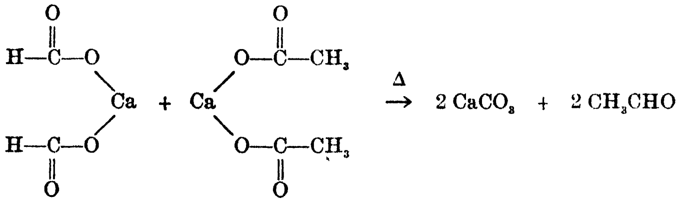


$$CH_3CH_2OH + [O] \rightarrow \left[CH_3\overset{OH}{\underset{H}{C}}-OH \right] \rightarrow CH_3CHO + H_2O$$

Ethyl alcohol

Acetaldehyde

Still another laboratory means of preparing acetaldehyde is to heat calcium acetate with calcium formate.



Calcium formate

Calcium acetate

Calcium carbonate

Acetaldehyde

Since the boiling point of the compound is so close to room temperature, the aldehyde must be collected in ether surrounded by ice.

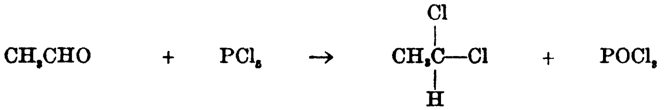
Industrially, acetaldehyde is obtained as a by-product of the fermentation of starch grains, particularly when the fermentation is carried out in the presence of sodium sulfite so as to yield a maximal amount of glycerol.

Another commercial source of acetaldehyde is from the reaction of acetylene and water, using sulfuric acid and mercuric sulfate as catalysts.

$$\underset{\text{Acetylene}}{C_2H_2} + H_2O \xrightarrow[\substack{HgSO_4 \\ 68^\circ\ C.}]{H_2SO_4} \underset{\text{Acetaldehyde}}{CH_3CHO}$$

Acetaldehyde undergoes all the reactions typical of aldehydes in general; therefore, its reactions will be used as typical of the chemical reactions of all aldehydes.

1. *Reaction with PCl_5.* In the chapter on Unsaturated Aliphatic Hydrocarbons, the reaction of acetaldehyde with phosphorus pentachloride was used in proving the structure of ethylene. The reaction again is useful in demonstrating that, in the structure of acetaldehyde, oxygen is combined with the terminal carbon by means of a double bond. Two chlorine atoms replace the oxygen of acetaldehyde in the reaction.

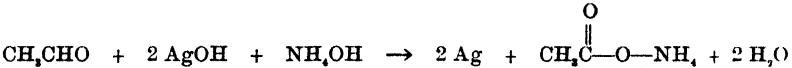


$$\underset{\text{Acetaldehyde}}{CH_3CHO} + \underset{\substack{\text{Phosphorus}\\ \text{pentachloride}}}{PCl_5} \rightarrow \underset{\substack{\text{Ethylidene}\\ \text{chloride}}}{CH_3\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}{-}Cl} + \underset{\substack{\text{Phosphorus}\\ \text{oxychloride}}}{POCl_3}$$

2. *Oxidation.* Acetaldehyde, on oxidation, forms an acid.

$$\underset{\text{Acetaldehyde}}{CH_3CHO} + [O] \rightarrow \underset{\text{Acetic acid}}{CH_3COOH}$$

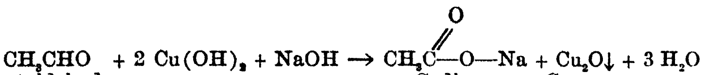
Because of their ease of oxidation, when aldehydes are warmed with an ammoniacal solution of silver nitrate, metallic silver precipitates out on the walls of the containing vessel.



$$\underset{\substack{\text{Acetalde-}\\ \text{hyde}}}{CH_3CHO} + \underset{\substack{\text{Silver}\\ \text{hydroxide}}}{2\,AgOH} + \underset{\substack{\text{Ammonium}\\ \text{hydroxide}}}{NH_4OH} \rightarrow \underset{\substack{\text{Metallic}\\ \text{silver}}}{2\,Ag} + \underset{\substack{\text{Ammonium}\\ \text{acetate}}}{CH_3\overset{\overset{\displaystyle O}{\|}}{C}{-}O{-}NH_4} + 2\,H_2O$$

This type of reaction is useful in the silvering of mirrors.

Aldehydes also are easily oxidized to the corresponding acid by Fehling's solution.* Copper oxide, a yellow to brick red precipitate, also results from the reaction.



$$\underset{\text{Acetaldehyde}}{CH_3CHO} + 2\,Cu(OH)_2 + NaOH \rightarrow \underset{\substack{\text{Sodium}\\ \text{acetate}}}{CH_3\overset{\overset{\displaystyle O}{/\!/}}{C}{-}O{-}Na} + \underset{\substack{\text{Cuprous}\\ \text{oxide}}}{Cu_2O\downarrow} + 3\,H_2O$$

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*Fehling's solution A contains sodium hydroxide and sodium potassium tartrate. Solution B contains copper sulfate. Equal parts of A and B are mixed together before making a test.

As will be noted later, the formation of mirrors and the oxidation of Fehling's solution are used as tests for distinguishing between aldehydes and ketones. Ketones under the same conditions are not oxidized.

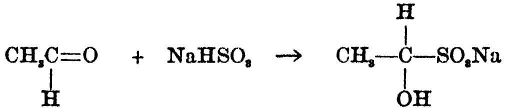
3. *Reduction.* Aldehydes, on reduction, yield primary alcohols.

$$\underset{\text{Acetaldehyde}}{CH_3CHO} \quad + \quad 2\,[H] \quad \begin{array}{c}\xrightarrow{\text{HCl + Fe}} \\ \xleftarrow{[O]}\end{array} \quad \underset{\text{Ethyl alcohol}}{CH_3CH_2OH}$$

This is the reverse of a process by which aldehydes can be prepared. With an increase in temperature the reaction shifts to the left, so that more aldehyde than alcohol is formed. At room temperature, however, hydrogen and a suitable catalyst will completely convert acetaldehyde to ethyl alcohol.

4. *Addition reactions.* Aldehydes undergo a number of addition reactions due to the presence of the carbonyl group containing a double bond. The student will find it helpful to remember that, as a general rule in these reactions, the positive part of the adding molecule (that is, the hydrogen atom or the metal) combines with the oxygen, while the remainder combines with the carbon. The addition takes place in this manner because actually the carbonyl group is definitely polar, the oxygen atom being relatively negative and the carbon atom relatively positive.

(a) *Addition of $NaHSO_3$.* When a cold, saturated solution of sodium bisulfite is added to acetaldehyde, a white, crystalline precipitate forms. The bisulfite addition products of the low molecular weight aldehydes are soluble in water, but are *insoluble in concentrated bisulfite solutions.*

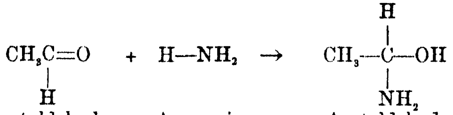


$$\underset{\text{Acetaldehyde}}{\underset{\displaystyle H}{CH_3\underset{|}{C}{=}O}} \quad + \quad \underset{\substack{\text{Sodium}\\\text{bisulfite}}}{NaHSO_3} \quad \rightarrow \quad \underset{\substack{\text{Acetaldehyde}\\\text{bisulfite compound}}}{CH_3{-}\overset{\displaystyle H}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}{-}SO_3Na}$$

Acetaldehyde Sodium bisulfite Acetaldehyde bisulfite compound

(b) *Addition of ammonia.* When dry ammonia is passed into an ethereal solution of an aldehyde, the aldehyde ammonia compound, which is insoluble in ether, precipitates.

When the solid addition product is heated with dilute acid, the pure aldehyde is regenerated.

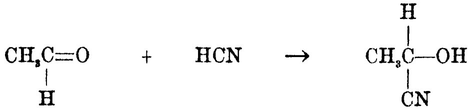


$$CH_3\underset{\displaystyle H}{C}{=}O + H{-}NH_2 \rightarrow CH_3{-}\overset{\displaystyle H}{\underset{\displaystyle NH_2}{C}}{-}OH$$

Acetaldehyde — Ammonia — Acetaldehyde ammonia compound

Acetaldehyde ammonia is available commercially in large quantities. It is used as an accelerator in the vulcanization of rubber and as a convenient solid form of aldehyde and ammonia for organic syntheses.

(c) *Addition of hydrogen cyanide.* Hydrogen cyanide added to aldehydes forms cyanohydrins.

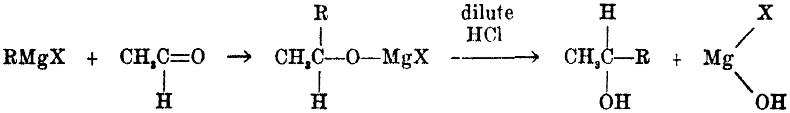


$$CH_3\underset{\displaystyle H}{C}{=}O + HCN \rightarrow CH_3\overset{\displaystyle H}{\underset{\displaystyle CN}{C}}{-}OH$$

Acetaldehyde — Hydrogen cyanide — Acetaldehyde cyanohydrin

The cyanohydrins are valuable compounds to the organic chemist, because the —C≡N, or nitrile group, is a potential COOH (carboxyl) group, characteristic of acids. Organic acids containing one more carbon atom than the aldehyde can be obtained from the cyanohydrins by hydrolysis with dilute acids or alkalies (see page 556). In this way, an hydroxy acid is obtained directly, and can combine with ammonia to yield an amino acid.

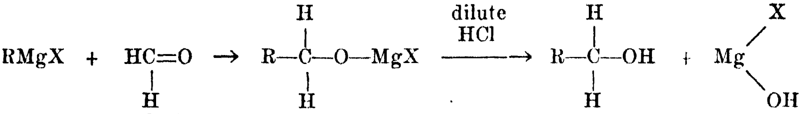
(d) *Reaction with Grignard reagent.* The usual reaction of aldehydes with Grignard reagents yields secondary alcohols. The first product of the reaction is a Grignard addition product, which can be decomposed by pouring it into a mixture of cracked ice and dilute hydrochloric acid, thus liberating the alcohol.



$$RMgX + CH_3\underset{\displaystyle H}{C}{=}O \rightarrow CH_3\overset{\displaystyle R}{\underset{\displaystyle H}{C}}{-}O{-}MgX \xrightarrow{\text{dilute HCl}} CH_3\overset{\displaystyle H}{\underset{\displaystyle OH}{C}}{-}R + Mg\begin{matrix}X\\OH\end{matrix}$$

A Grignard reagent — Acetaldehyde — Grignard addition product — A secondary alcohol

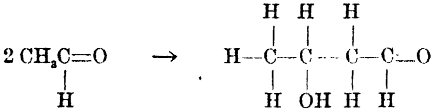
Since formaldehyde contains two hydrogens on the carbonyl group, a primary alcohol results from its reaction with Grignard reagent.



$$\mathrm{RMgX} + \underset{\underset{\mathrm{H}}{|}}{\mathrm{HC{=}O}} \rightarrow \mathrm{R{-}}\overset{\overset{\mathrm{H}}{|}}{\underset{\underset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}O{-}MgX} \xrightarrow{\text{dilute HCl}} \mathrm{R{-}}\overset{\overset{\mathrm{H}}{|}}{\underset{\underset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}OH} + \mathrm{Mg}\begin{matrix}\diagup \mathrm{X}\\ \diagdown \mathrm{OH}\end{matrix}$$

Formaldehyde A primary alcohol

(e) *Aldol condensation.* An important type of reaction takes place when acetaldehyde is treated with calcium hydroxide or zinc chloride. The resulting product is a condensation compound in which one molecule of acetaldehyde has combined with the other.

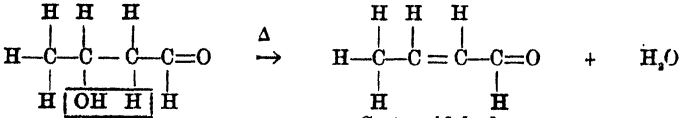


$$2\,\mathrm{CH_3}\underset{\underset{\mathrm{H}}{|}}{\mathrm{C{=}O}} \rightarrow \mathrm{H{-}}\overset{\overset{\mathrm{H}}{|}}{\underset{\underset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}}\overset{\overset{\mathrm{H}}{|}}{\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}}\mathrm{{-}}\overset{\overset{\mathrm{H}}{|}}{\underset{\underset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}}\underset{\underset{\mathrm{H}}{|}}{\mathrm{C{=}O}}$$

Acetaldehyde 3-Hydroxybutanal or aldol

Condensation can be defined as the union of two or more molecules to form a carbon-to-carbon linkage, usually with the elimination of some such small molecule as water or ammonia. The molecules need not be necessarily of the same type. The substance, 3-hydroxybutanal, formed by the condensation of acetaldehyde with itself, shows characteristics of both an *alde*hyde and an alcoh*ol;* hence the name, *aldol,* for this particular kind of condensation.

Aldol readily loses water to give an unsaturated aldehyde, crotonaldehyde. In the laboratory this can be brought about by gentle heating.

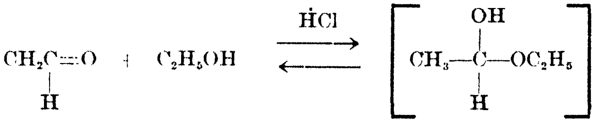


$$\mathrm{H{-}}\overset{\overset{\mathrm{H}}{|}}{\underset{\underset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}}\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}\mathrm{{-}}\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}\mathrm{{-}}\underset{\underset{\mathrm{H}}{|}}{\mathrm{C{=}O}}\ \ \boxed{\mathrm{OH\ \ H}} \xrightarrow{\Delta} \mathrm{H{-}}\overset{\overset{\mathrm{H}}{|}}{\underset{\underset{\mathrm{H}}{|}}{\mathrm{C}}}\mathrm{{-}}\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}\mathrm{{=}}\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}\mathrm{{-}}\underset{\underset{\mathrm{H}}{|}}{\mathrm{C{=}O}} + \mathrm{H_2O}$$

Aldol Crotonaldehyde

Aldol condensation reactions are general for all aldehydes containing an alpha hydrogen, that is, a hydrogen on the carbon adjacent to the carbonyl group. The reaction is important in synthetic work for building up long chain carbon compounds. There is some evidence that the aldol condensation is one of the means by which plants build up complex compounds. The loss of water from the product of aldol condensation, followed by the subsequent addition of ammonia to the double bonds, may be a mechanism for the formation of the physiologically important class of compounds known as alkaloids (see Chapter XX).

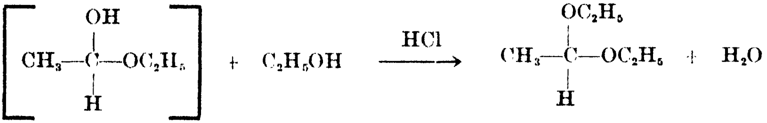
(f) *Formation of acetals.* In the presence of a very small amount of an acid, acetaldehyde reacts with alcohols to form acetals. The first product of the addition of an alcohol to an aldehyde is an ether-alcohol known as *hemiacetal.* Because of the rapidity with which hemiacetals revert to mixtures of aldehyde and alcohol, only a few hemiacetals have been isolated. As a rule they exist only in solution.



$$\underset{\displaystyle H}{CH_2C{=}O} + C_2H_5OH \overset{HCl}{\rightleftarrows} \left[CH_3-\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}-OC_2H_5\right]$$

Acetaldehyde Ethanol Acetaldehyde hemiacetal
Ethanol

In the presence of a mineral acid, the hemiacetal reacts with another molecule of alcohol, through elimination of a molecule of water, to form the *acetal.*



$$\left[CH_3-\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}-OC_2H_5\right] + C_2H_5OH \xrightarrow{HCl} CH_3-\overset{\displaystyle OC_2H_5}{\underset{\displaystyle H}{C}}-OC_2H_5 + H_2O$$

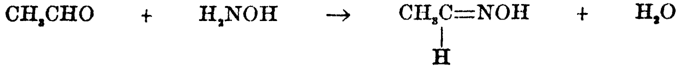
Acetal or
1,1-diethoxyethane

The acetals are hydrolyzed to aldehydes by acids but they are stable to alkalies. Hemiacetals and acetals are of special interest because the cyclic form of glucose (page 328) can be considered to be a hemiacetal.

Acetals are useful in syntheses when it is desired to protect the aldehyde group from the action of an oxidizing agent or an alkali. At the end of the synthesis the aldehyde group may be restored by acid hydrolysis of the acetal.

5. *Reactions in which carbonyl oxygen is lost.*

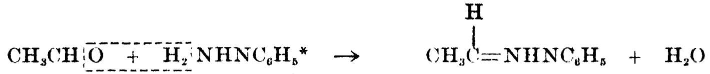
(a) *Reaction with hydroxylamine.* The reaction of hydroxylamine with aldehydes results in the formation of solid, crystalline compounds called oximes. Each oxime has a definite melting point that is characteristic of the particular aldehyde from which it is derived. For this reason, oximes are useful in the identification of aldehydes.



$$CH_3CHO \quad + \quad H_2NOH \quad \rightarrow \quad \underset{\substack{|\\H}}{CH_3C}{=}NOH \quad + \quad H_2O$$

Acetaldehyde Hydroxylamine Acetaldoxime

(b) *Reaction with phenylhydrazine.* Another means of identifying aldehydes is by their reaction with phenylhydrazine. Again a characteristic crystalline derivative, termed a phenylhydrazone, is formed.



$$CH_3CH\boxed{O \;+\; H_2}NHNC_6H_5{}^{*} \quad \rightarrow \quad \overset{\substack{H\\|}}{CH_3C}{=}NHNC_6H_5 \quad + \quad H_2O$$

Acetaldehyde Phenylhydrazine Phenylhydrazone of acetaldehyde

A melting point determination is easily carried out in the laboratory by placing the organic substance in a glass capillary tube about the size of a darning needle. The tube is held alongside a thermometer, usually by means of a rubber band, and both are immersed in a melting point bath of some liquid with a high boiling point. The temperature of the bath is slowly increased, and the temperature at which the substance in the capillary tube liquefies is carefully noted. If the substance is pure, it all will melt at one temperature or within a very narrow range.

The melting points of the oxime and the phenylhydrazone derivative of all the common aldehydes have been determined and are recorded in tabular form in handbooks. Thus, if a mixture of substances gives a positive test for the presence of an aldehyde, the aldehyde present can be identified by forming a solid oxime or phenylhydrazone derivative, determining the melting point of this solid, and comparing it with recorded values. If the aldehyde is one that has never been characterized before, it is then necessary to go through the long process of quantitative analysis and molecular weight determination to identify the aldehyde.

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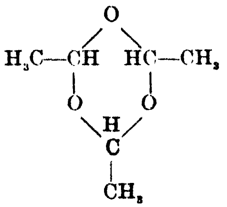
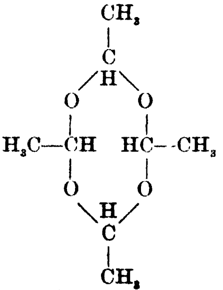
*The C_6H_5-group, or radical that is known as the phenyl group, is derived from benzene. This aromatic hydrocarbon will be discussed in Chapter XVI.

6. *Polymerization.** If acetaldehyde is treated with a few drops of concentrated sulfuric acid, it polymerizes violently to paraldehyde, a liquid insoluble in water and with a boiling point of 124° C. Paraldehyde shows none of the reactions typical of aldehydes. Acetaldehyde is regenerated when paraldehyde is heated with dilute acids. Frequently acetaldehyde is transported in the form of this polymer, because paraldehyde is neither as volatile nor as inflammable as acetaldehyde. Paraldehyde is used occasionally as an anodyne in childbirth. It also is used as a soporific, particularly in the treatment of patients with mental diseases.

Another polymerization product is metaldehyde, formed when acetaldehyde is treated with acid at a low temperature. Like paraldehyde, metaldehyde shows none of the chemical properties characteristic of aldehydes. It, too, can be converted back into the original substance by distillation with dilute acid. Ring structures that account for their lack of aldehyde properties have been proposed for paraldehyde and metaldehyde, since these proposed structures contain no carbonyl groups.



Paraldehyde



Metaldehyde

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*Polymerization, as mentioned previously, is the combination of a number of identical molecules to give a larger molecule.

When acetaldehyde and the other lower members of the aldehyde series (except formaldehyde) are treated with a strong base, such as 10 per cent sodium or potassium hydroxide, they polymerize to form gumlike substances called aldehyde resins. The exact chemical composition of these resins has not been definitely established.

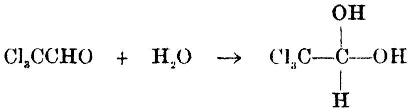
7. *Fuchsine test for aldehydes.* The use of Schiff's reagent furnishes a sensitive color test for the presence of aldehydes. This reagent is prepared by dissolving an organic dye, fuchsine or magenta, in water and decolorizing this solution by adding sodium bisulfite, followed by a few cubic centimeters of concentrated hydrochloric acid. To test for an aldehyde, a small amount of solution is poured into the decolorized dye solution. If an aldehyde is present, a brilliant red color develops. Ketones do not give this reaction.

8. *Reaction with halogens.* Acetaldehyde and the higher aldehydes react directly with the halogens, bromine and chlorine, by substitution of one or more hydrogen atoms on the carbon adjacent to the carbonyl group.

$$\underset{\text{Acetaldehyde}}{CH_3CHO} + 3\,Cl_2 \rightarrow \underset{\text{Chloral}}{Cl_3C\text{—}CHO} + 3\,HCl$$

The fully chlorine-substituted acetaldehyde is known as chloral, or trichloroacetaldehyde. This compound, which is an oily liquid with an odor much like acetaldehyde, is the most important of the chlorinated aldehydes. Since it contains the carbonyl group, chloral shows chemical behavior typical of aldehydes. Commercially, chloral is not prepared by the direct chlorination of acetaldehyde, but rather by the reaction of alcohol and chlorine. The oxidation of the alcohol by chlorine is the first step in the synthesis, and then the chlorination of the aldehyde proceeds as in the foregoing reaction. Chloral is used in the preparation of DDT, the widely known insecticide (page 415).

On boiling with water, chloral forms chloral hydrate, which crystallizes in large, clear crystals readily soluble in water. Chloral hydrate is one of the few stable compounds containing two hydroxyl groups on one carbon atom. Probably this is due to the three strong electronegative groups (i.e., three chlorine atoms) on the carbon adjacent to the carbonyl group.



$$Cl_3CCHO + H_2O \rightarrow Cl_3C-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-OH$$

Chloral Chloral hydrate

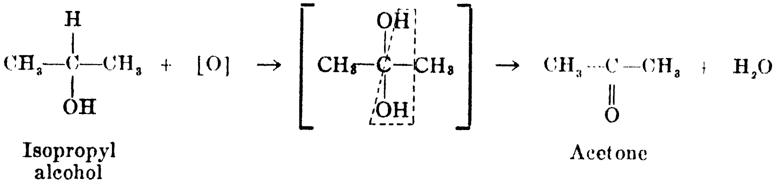
The hydrate is more stable than chloral. It finds use in medicine as a hypnotic and, in large doses, as an anesthetic. Both chloral and chloral hydrate can be converted into chloroform by heating with alkali.

The chemical reactions of acetaldehyde have been discussed at length because they are type reactions that are characteristic of all aldehydes.

Uses of acetaldehyde. Reference already has been made to the use of acetaldehyde in the form of paraldehyde, and to a number of synthetic reactions. In addition, paraldehyde is useful in the synthesis of substances that hasten the vulcanization of rubber and in the manufacture of synthetic resins. The production of acetic acid and acetone consumes large quantities of acetaldehyde. Smaller amounts are used in the manufacture of drugs and in silvering mirrors. Over 351 million pounds of acetaldehyde were produced in the United States in 1946.

Ketones.—As was mentioned at the beginning of this chapter, oxidation of secondary alcohols yields ketones, products containing the carbonyl group and having the type formula $R-\underset{\underset{\displaystyle O}{\|}}{C}-R'$. It will be noted that they differ from aldehydes in having an R group instead of a hydrogen atom attached to the carbonyl group. The R and R′ can be the same or different alkyl radicals, thus permitting the existence of both simple and mixed ketones. According to the International system of nomenclature, ketones have an *one* ending instead of the final *e* in the paraffin hydrocarbon name. The simplest and commonest ketone, therefore, is called 2-propanone by the I.U.C. system. The more commonly used name is acetone. Another system names the alkyl groups attached to the carbonyl, and calls acetone, dimethyl ketone.

Acetone.—Acetone is an organic compound of very great commercial importance. The large quantities necessary to meet the needs of industry are produced by several different methods. One important method, and the one that illustrates that secondary alcohols yield ketones on oxidation, is the oxidation of isopropyl alcohol to form acetone. The isopropyl alcohol is made from propylene, most of which results from the cracking process. The oxidation can be carried out by blowing air through a hot solution of the alcohol and passing the vapors over a catalyst.



$$CH_3-\underset{OH}{\overset{H}{C}}-CH_3 + [O] \rightarrow \left[CH_3-\underset{OH}{\overset{OH}{C}}-CH_3\right] \rightarrow CH_3-\underset{\underset{O}{\|}}{C}-CH_3 + H_2O$$

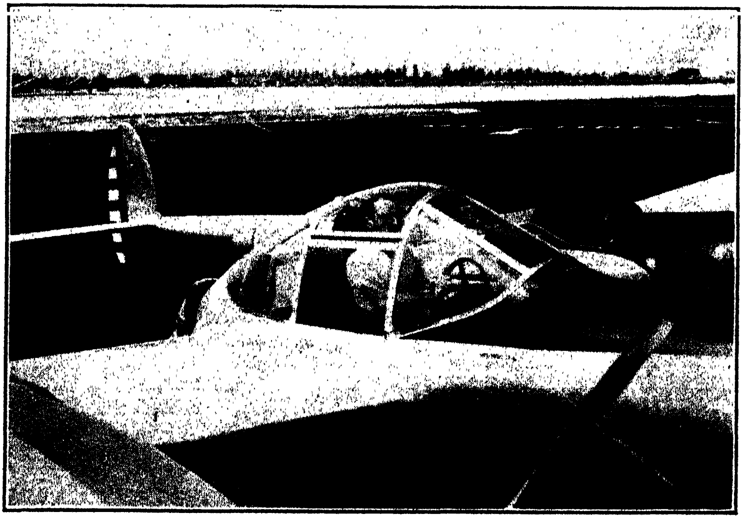
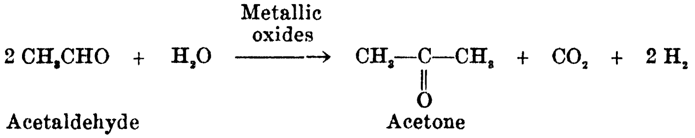


Fig. 27.—Acetone is an essential chemical in the manufacture of the plastic for the Plexiglas (methyl methacrylate) cockpit enclosure on the Lockheed P-38, which is a high-powered, heavily armed army fighter plane. The permanent clarity, light weight, and high impact strength of Plexiglas make it well suited for such uses on aircraft. (Courtesy of the Röhm and Haas Co., Inc.)

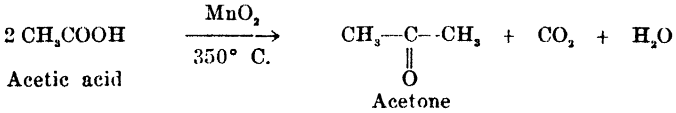
Another important source of acetone is acetaldehyde, which is made by passing acetylene into dilute sulfuric acid containing mercuric sulfate. The acetaldehyde vapor is mixed with steam and passed over heated metallic oxides to convert it to acetone.



$$\underset{\text{Acetaldehyde}}{2\,CH_3CHO} + H_2O \xrightarrow{\text{Metallic oxides}} \underset{\text{Acetone}}{CH_3\text{—}\underset{\displaystyle O}{\underset{\|}{C}}\text{—}CH_3} + CO_2 + 2\,H_2$$

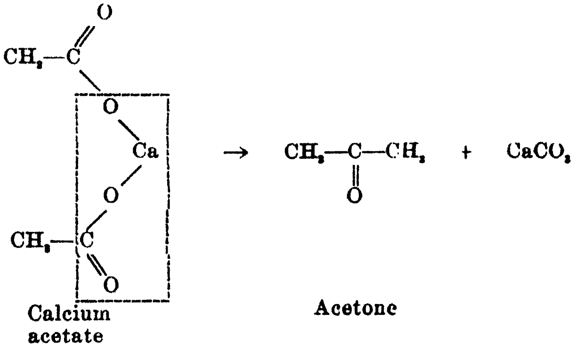
Large quantities of acetone are made by the fermentation of corn starch or molasses by microorganisms to give acetone and butyl alcohol in the ratio of one to two. This process was developed during the first World War because other sources were insufficient to meet the demand for the acetone used in the manufacture of smokeless powder and "dopes" for airplane wings.

Acetone is present to the extent of 0.5 per cent in the distillate from the destructive distillation of wood. The principal distillation product is acetic acid, which, if desired, can be converted into acetone.



$$\underset{\text{Acetic acid}}{2\,CH_3COOH} \xrightarrow[350°\ C.]{MnO_2} \underset{\text{Acetone}}{CH_3\text{—}\underset{\displaystyle O}{\underset{\|}{C}}\text{—}CH_3} + CO_2 + H_2O$$

In the laboratory, acetone can be prepared by the distillation of calcium or barium acetate.



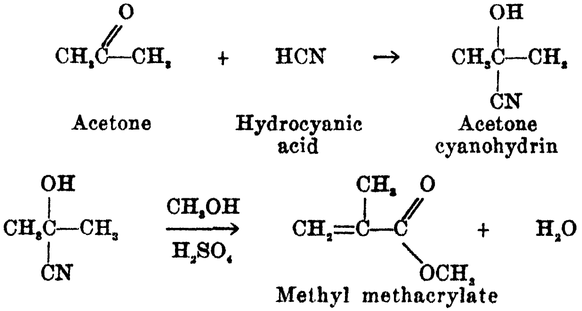
As to physical properties, acetone is a water-clear liquid with an odor characteristic of nail polish remover. It is soluble in water, alcohol, and ether in all proportions.

Acetone is found in traces in normal blood and urine. In persons suffering from diabetes mellitus, the amount is greatly increased in the blood and expired air, especially when the person is nearing a state of diabetic coma.

Many of the chemical reactions of aldehydes and ketones are similar. In general, the reactions do not take place as readily with ketones as with the aldehydes. The accompanying summary of chemical reactions is used to illustrate the similarity and differences between aldehydes and ketones.

Uses of acetone. Acetone finds wide usage as a solvent for a variety of products, such as gums, resins, lacquers, plastics, acetylene, and gun cotton. In the process of manufacturing the British brand of smokeless powder known as Cordite, acetone is used as a solvent. Nail polish removers and paint and varnish removers contain acetone. Sometimes acetone is used as a denaturant for ethyl alcohol. It is a raw material in the manufacture of chloroform, iodoform, sulfonal (a sleep-producing drug), plastics, and resins. It has been estimated that the production of acetone in the United States in 1946 amounted to over 335 million pounds.

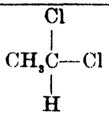
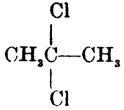
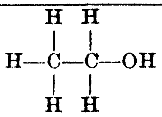
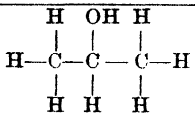
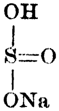
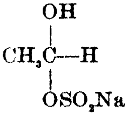
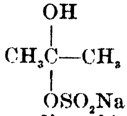
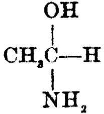
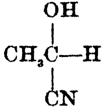
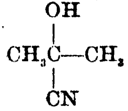
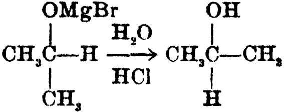
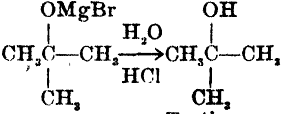
Large quantities of acetone are being used in the production of the methyl methacrylate type of plastics, sold under the trade names of "Lucite" and "Plexiglas." The equations for the preparation of methyl methacrylate are:



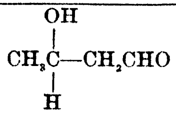
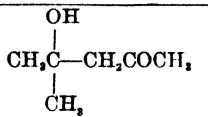
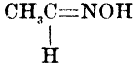
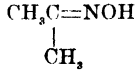
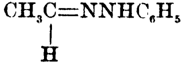
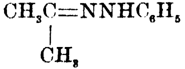
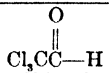
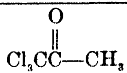
$$CH_3\overset{O}{\overset{/\!\!/}{C}}-CH_3 + HCN \rightarrow CH_3\overset{OH}{\underset{CN}{C}}-CH_3$$

$$CH_3\overset{OH}{\underset{CN}{C}}-CH_3 \xrightarrow[H_2SO_4]{CH_3OH} CH_2=\overset{CH_3}{C}-C(=O)OCH_3 + H_2O$$

Summary of Chemical Reactions

REAGENT OR REACTION	ORGANIC COMPOUND FORMED, OR THE RESULT OF REACTION, WITH *acetaldehyde*	ORGANIC COMPOUND FORMED, OR THE RESULT OF REACTION, WITH *acetone*
PCl_5 1. Phosphorus pentachloride	 $CH_3\overset{Cl}{\underset{H}{C}}{-}Cl$ Ethylidene chloride	 $CH_3\overset{Cl}{\underset{Cl}{C}}{-}CH_3$ 2,2-dichloropropane
2. Mild oxidation	Reduces $AgNO_3$ and Fehling's solution	Does not reduce $AgNO_3$ or Fehling's solution
3. Strong oxidizing agents (H_2SO_4 + $K_2Cr_2O_7$)	CH_3COOH Acetic acid	Decomposition products, mixture of acids with fewer carbon atoms
4. Reduction	 $H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-OH$ Primary alcohol	 $H-\overset{H}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-H$ Secondary alcohol
5. Addition reactions  $\overset{OH}{\underset{ONa}{S}}{=}O$ (a) Sodium bisulfite	 $CH_3\overset{OH}{\underset{OSO_2Na}{C}}{-}H$ Acetaldehyde sodium bisulfite addition product	 $CH_3\overset{OH}{\underset{OSO_2Na}{C}}{-}CH_3$ Acetone sodium bisulfite addition product
NH_3 (b) Ammonia	 $CH_3\overset{OH}{\underset{NH_2}{C}}{-}H$ Acetaldehyde ammonia	No similar reaction
HCN (c) Hydrocyanic acid	 $CH_3\overset{OH}{\underset{CN}{C}}{-}H$ Acetaldehyde cyanohydrin	 $CH_3\overset{OH}{\underset{CN}{C}}{-}CH_3$ Acetone cyanohydrin
CH_3MgBr (d) Grignard reagent	 $CH_3\overset{OMgBr}{\underset{CH_3}{C}}{-}H \xrightarrow[HCl]{H_2O} CH_3\overset{OH}{\underset{H}{C}}{-}CH_3$ Secondary alcohol	 $CH_3\overset{OMgBr}{\underset{CH_3}{C}}{-}CH_3 \xrightarrow[HCl]{H_2O} CH_3\overset{OH}{\underset{CH_3}{C}}{-}CH_3$ Tertiary alcohol

SUMMARY OF CHEMICAL REACTIONS—*Continued*

REAGENT OR REACTION	ORGANIC COMPOUND FORMED, OR THE RESULT OF REACTION, WITH *acetaldehyde*	ORGANIC COMPOUND FORMED, OR THE RESULT OF REACTION, WITH *acetone*
$Ca(OH)_2$ (e) Aldol condensation	 $CH_3\overset{OH}{\underset{H}{C}}—CH_2CHO$ Aldol	 $CH_3\overset{OH}{\underset{CH_3}{C}}—CH_2COCH_3$ Diacetone alcohol
6. Reactions in which carbonyl oxygen is lost		
NH_2OH (a) Hydroxylamine	 $CH_3\underset{H}{C}=NOH$ Acetaldoxime	 $CH_3\underset{CH_3}{C}=NOH$ Acetketoxime
$C_6H_5NHNH_2$ (b) Phenylhydrazine	 $CH_3\underset{H}{C}=NNHC_6H_5$ Acetaldehyde phenylhydrazone	 $CH_3\underset{CH_3}{C}=NNHC_6H_5$ Acetone phenylhydrazone
7. Polymerization	$(CH_3CHO)_3$ Paraldehyde	Does not polymerize
8. Fuchsine test	Red color, positive test	Negative test
9. Halogens	 $Cl_3C\overset{O}{\overset{\|}{C}}—H$ Chloral	 $Cl_3C\overset{O}{\overset{\|}{C}}—CH_3$ Trichloroacetone

Resins used for the manufacture of plastics are obtained by polymerization of methyl methacrylate under the influence of heat, light, oxygen, or oxygen-yielding substances, such as hydrogen peroxide and sodium peroxide. Such properties as crystal clarity, strength, weather resistance, and unlimited color possibilities have led to an ever-widening use of methyl methacrylate plastics. Dentures made from this material have been so well received that they have replaced practically all other plastics for this purpose. Dental plates made from acrylate resins can be pigmented to simulate the color of the mouth tissues and, in addition, the teeth are strong, durable, and water resistant. Other uses for methyl methacrylate plastics are for furniture, reflector buttons on highways, costume jewelry,

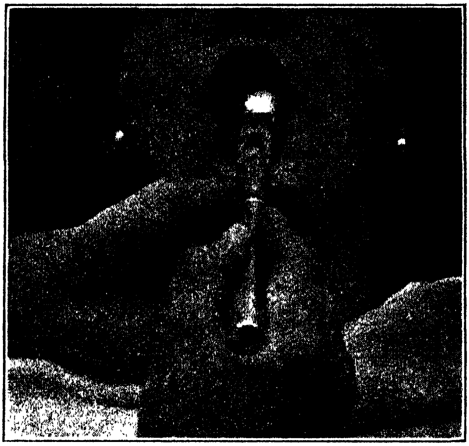


Fig. 28.—A tongue depressor made of a curved Lucite (methyl methacrylate) rod with concentrated cold light coming out at the end. The light is conveyed by internal reflection from a tiny bulb in the end of the instrument around the curve of the depressor. The solid, transparent methyl methacrylate resin rod functions like mirrors, and through the rod light can be "piped" to wherever desired. Such a method is used in the airplane factories, especially to facilitate night work, in the examination of otherwise inaccessible parts of machinery. (Courtesy of the Du Pont Co.)

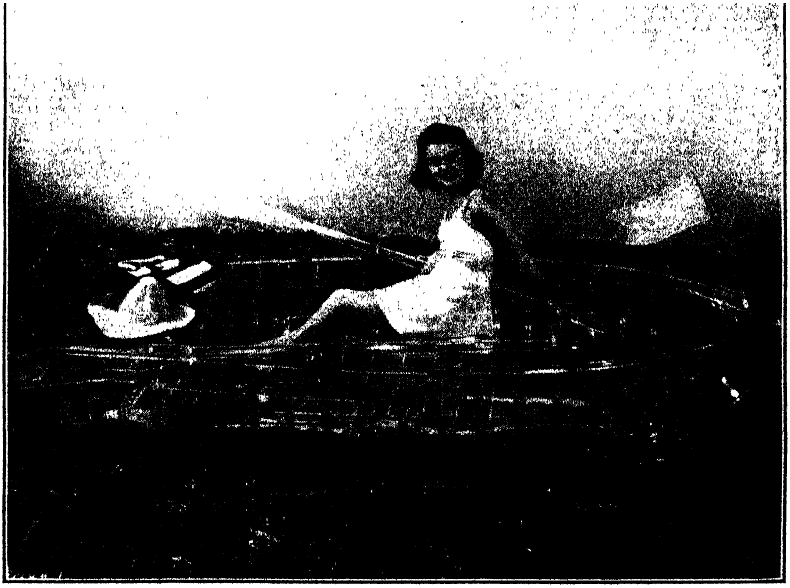


Fig. 29.—The first plastic rowboat ever to be made entirely of Du Pont's "Lucite" (methyl methacrylate). The boat is 8 feet 6 inches long and weighs 96 pounds. Although shown above on an "ocean" of cellophane, actual tests have proved it to be seaworthy. (Courtesy of the Du Pont Style News Service.)

automobile fixtures, and contact lenses. These transparent resins are used extensively by the aircraft industry for cockpit enclosures, observation hatches, and bomber nose sections. Methacrylate resins have been used for the permanent preservation of agricultural and biological specimens in their natural color. A beautiful butterfly thus preserved makes an attractive watch charm. Transparent surgical splints have been made of Lucite.

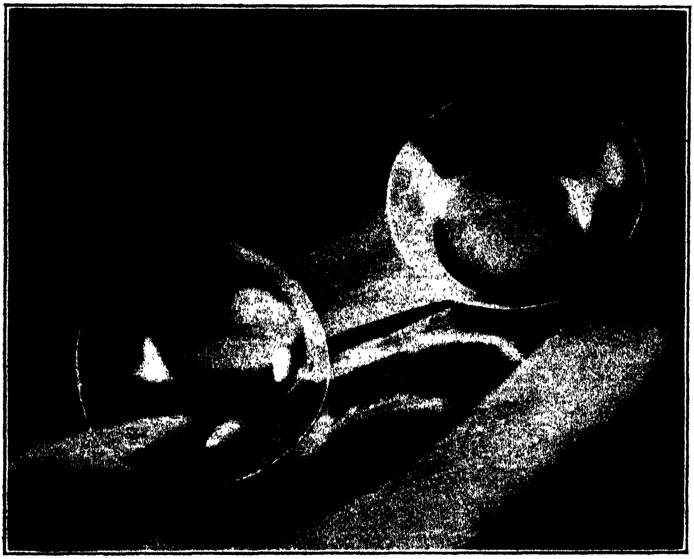


Fig. 30.—Plexiglas (methyl methacrylate) contact lenses, formed and ground by Obrig Laboratories. Optometrists are making these contact lenses by forming the plastic to fit the patient's eyeball and then grinding the corneal section of the lens to the proper corrective curvature. Light in weight, durable, and nontoxic Plexiglas lenses are worn by engineers and others for whom the condensation of moisture on ordinary glasses in winter is an inconvenience or actual menace to safety. Pigmented contact lenses have been used successfully by motion picture actors to change the color of their eyes from blue to brown when this was necessary for Technicolor films. (Courtesy of the Röhm and Haas Co., Inc.)

Other Ketones.—Methyl ethyl ketone or butanone-2 is a by-product of the production of acetone by the destructive distillation of calcium acetate. This ketone can be prepared conveniently on a commercial scale from the gases that result from the cracking process. Butene-1 or butene-2 is absorbed in sulfuric acid, and the butyl alcohol formed is then oxidized to methyl ethyl ketone. It has a higher boiling point than acetone, and is used as a solvent when a less volatile compound than acetone is indicated. Methyl ethyl ketone is widely used in the solvent dewaxing process for refining lubricating oils.

Biacetyl, $CH_3CO \cdot COCH_3$, is a diketone. It is a greenish-yellow liquid that is the main flavoring component of butter, in which it is present to the extent of 0.7 to 1.5 parts per million. This compound is sometimes used to give a butter flavor to butter substitutes, such as margarines and certain hydrogenated fats.

In general, the higher ketones that are important enough to be manufactured on an industrial scale are used as solvents.

Study Questions

1. What is the type formula for an aldehyde and for a ketone? What is the name of the characteristic group present in each type of compound?
2. Suppose you have a water-clear liquid that is known to be an aldehyde or a ketone. Describe in some detail, or give an equation that will show how you can determine whether the substance is an aldehyde or a ketone.
3. What is the common name of a 40 per cent solution of methanal?
4. Suppose you have a mixture of ethan*ol* and ethan*al*. Give the equation or equations for a method of separating these compounds from each other by chemical means.
5. Write the equation for the reaction of acetone with phenylhydrazine.
6. What is meant by the term *aldol condensation?* Illustrate the reaction with an equation.
7. What are two uses of formaldehyde?
8. Aldehydes are the oxidation products of what class of alcohols? What class of alcohols give ketones on oxidation?
9. What are some of the chemical reactions that methanal undergoes that its homologues do not?
10. Name five articles made of the formaldehyde-phenol type of plastic.
11. What is meant by *polymerization?* What are two polymerization products of formaldehyde?
12. What is a commercial method of preparing acetone? List three uses of this product.
13. What is the name of fully chlorinated acetaldehyde? For what is the compound used?
14. Write the equation for the reactions involved in the formation of methyl methacrylate, the raw material in the manufacture of "Lucite" and "Plexiglas" plastics.

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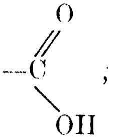
CHAPTER IX

SATURATED MONOBASIC ACIDS AND THEIR DERIVATIVES

Introduction.—Organic acids constitute a large and interesting group of compounds which have many uses in industry and the domestic arts. The characteristic group of organic acids,  $-C{=}O(OH)$, is known as the carboxyl or carboxy radical. For convenience in printing, this group often is written as —COOH, but the student should use the graphic formula in writing equations. It will be seen that the group contains both a carbonyl and an hydroxyl group. The name *carboxyl* is indicative of this fact, since it is formed from the terms *carb*onyl and hydr*oxyl*. The presence of the carbonyl group modifies the behavior of the hydroxyl group so that its reactions are quite different from its reaction in compounds such as the alcohols. The hydrogen on the hydroxyl group is held much less firmly, and, in aqueous solutions, the hydrogen separates (ionizes) to give a positively charged hydrogen ion and a negatively charged radical or anion. This is a characteristic of all acids. In fact, in physical chemistry, one definition of an acid is "a substance that yields hydrogen ions in aqueous solution." The sour taste of acids is due to the presence of the hydrogen ion.

Organic acids as a group are not as strong as inorganic acids. In other words, in water solutions the percentage of an organic acid present as hydrogen ions is smaller than would be the case for an equal concentration of an inorganic acid. But the organic acids are like the inorganic acids in their ability to neutralize bases to form salts.

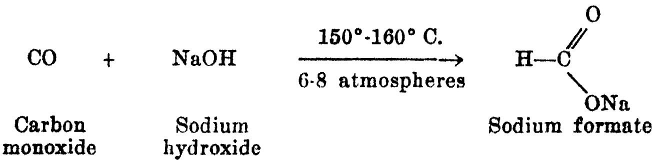
The organic acids to be considered first are known as monocarboxylic or monobasic acids, since they contain one carboxyl group. One molecule of these acids will neutralize one molecule of a monovalent base; hence the name, monobasic, for the group. This homologous series usually is referred to as the fatty acid series, because the acids containing four and more carbon atoms are constituents of the natural fats, from which they can be obtained by hydrolysis. The general formula for the series is $C_nH_{2n+1}COOH$. Reference to Table X will show that many of the names suggest common sources of the acids, but the official names according to the I.U.C. system are obtained by dropping the final *e* in the name of the paraffin hydrocarbon with the same number of carbon atoms and adding instead *oic*.

TABLE X

CONSTANTS OF SOME NORMAL SATURATED MONOBASIC ACIDS

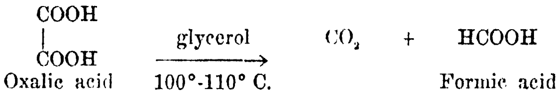
COMMON NAME	FORMULA	M.P. ° C.	B.P. ° C.
Formic	$HCOOH$	8.4	100.7
Acetic	CH_3COOH	16.6	118.1
Propionic	C_2H_5COOH	-22.0	141.1
Butyric	C_3H_7COOH	- 7.9	163.5
Valeric	C_4H_9COOH	-34.5	187.0
Caproic	$C_5H_{11}COOH$	- 2.0	205.0
Caprylic	$C_7H_{15}COOH$	16.0	237.5
Capric	$C_9H_{19}COOH$	31.5	268.4
Lauric	$C_{11}H_{23}COOH$	44.0	----
Myristic	$C_{13}H_{27}COOH$	58.0	----
Palmitic	$C_{15}H_{31}COOH$	64.0	----
Stearic	$C_{17}H_{35}COOH$	69.4	383.0
Arachidic	$C_{19}H_{39}COOH$	76.3	328.0

Formic Acid, HCOOH.—Methanoic or formic acid, the simplest member of the fatty acid series, was obtained first by the distillation of red ants. The reason for carrying out this experiment now is obscure, but the experiment inspired the name for the compound. (*Formica* is the Latin term for ant.)


$$CO + NaOH \xrightarrow[\text{6-8 atmospheres}]{150°\text{-}160° C.} H\!-\!C(=O)ONa$$

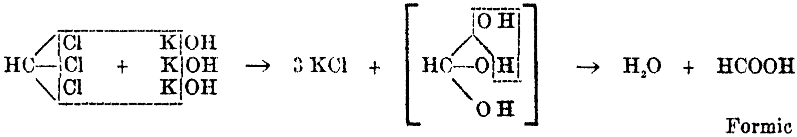
Formic acid is prepared commercially by the reaction of carbon monoxide with solid sodium hydroxide at temperatures of 150° to 160° C. and under a pressure of 6 to 8 atmospheres. The acid of commerce, which is 85 per cent formic acid, is obtained from the sodium formate by distillation with sulfuric acid. Because concentrated sulfuric acid dehydrates formic acid with the evolution of carbon monoxide, special manipulations are necessary in the recovery of formic acid from sodium formate.

A laboratory method for preparing formic acid involves the heating of oxalic acid with glycerol. A number of intermediate products are formed, but the reaction consists essentially in the decomposition of the oxalic acid to yield carbon dioxide and formic acid.



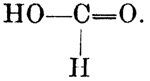
$$\underset{\text{Oxalic acid}}{\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{COOH}\end{array}} \xrightarrow[\text{100°-110° C.}]{\text{glycerol}} CO_2 + \underset{\text{Formic acid}}{HCOOH}$$

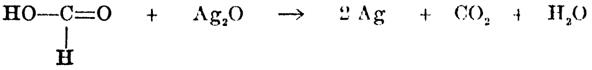
Another laboratory means for preparing formic acid is by the action of a strong base on one of the trihalogen derivatives of methane (chloroform, bromoform, or iodoform).



Chloroform Potassium hydroxide Potassium chloride Intermediate product Formic acid

Formic acid is a colorless liquid with a penetrating, pungent odor. It mixes in all proportions with water, alcohol, and ether. If the concentrated acid comes in contact with the skin, painful blisters result.

Chemical properties. The chemical properties of formic acid, as is true of the chemical properties of the first member of many homologous series, differ in several particulars from those of other members of the series. Formic acid is distinctive as compared with its homologues in that it exhibits the properties of an aldehyde. The reason can be seen if the formula is written as  $\underset{\displaystyle H}{HO—\overset{}{C}=O}$. Its reducing action is illustrated by its reactions with silver compounds to form a silver mirror.



$$\underset{\displaystyle H}{HO—C=O} + Ag_2O \rightarrow 2\,Ag + CO_2 + H_2O$$

Formic acid Silver oxide Metallic silver

Formic acid is dehydrated easily. For example, when it is heated with sulfuric acid, carbon monoxide and water are obtained.

$$\underset{\text{Formic acid}}{HCOOH} \xrightarrow[H_2SO_4]{\Delta} \underset{\text{Carbon monoxide}}{CO} + H_2O$$

This reaction furnishes a convenient laboratory method for preparing small quantities of *pure* carbon monoxide. Carbon monoxide when prepared by other methods usually is contaminated with carbon dioxide.

Formic acid is less stable than the other acids in the same homologous series. When it is heated above 160° C., it decomposes to form carbon dioxide and hydrogen.

$$HCOOH \xrightarrow{+160^\circ\ C.} CO_2 + H_2$$

The ionization constant of an acid, which is determined by the percentage of the acid that is ionized, indicates the strength of an acid. The ionization constant of formic acid shows that it is twelve times as strong as its next homologue, acetic acid.

An important salt of formic acid, sodium formate, reacts in a manner different from the corresponding salts of the other acids in the same series. When sodium formate is heated, hydrogen is evolved and sodium oxalate results. This is an important method for the preparation of oxalic acid.

$$\underset{\text{Sodium formate}}{2\,HCOONa} \xrightarrow{\Delta} H_2 + \underset{\text{Sodium oxalate}}{NaOOC—COONa}$$

Uses. Formic acid is important in the tanning industry, where it is employed to neutralize the lime (calcium hydroxide) used in dehairing hides. Because formic acid has the lowest molecular weight of any of the organic acids, pound for pound it will neutralize more of a base than any other organic acid. As the commercial production of formic acid increases, the price of the acid is becoming lower. Accordingly, it is replacing the other organic acids, such as acetic, for various industrial purposes.

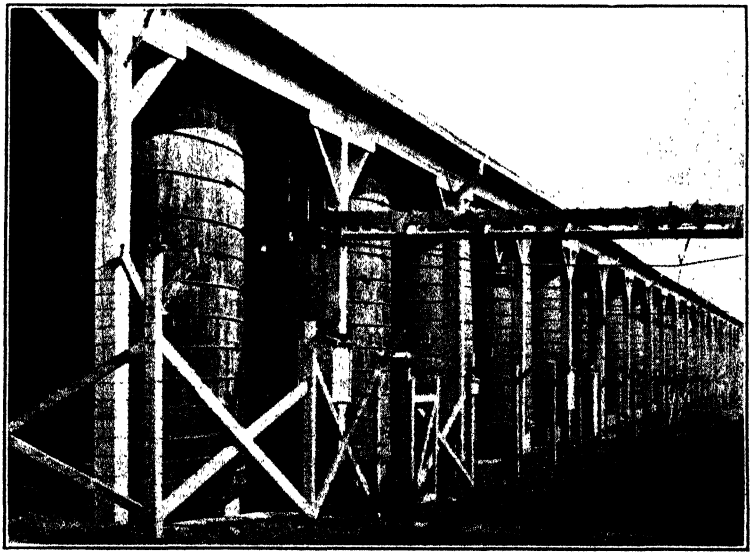


Fig. 31.—Tanks in which cider vinegar is aged. The apple juice imparts to this type of vinegar characteristic flavors and odors that are not found in vinegars made from ethyl alcohol by the "quick vinegar process." Good cider vinegar is as carefully produced as fine old wine. (Courtesy of the H. J. Heinz Co.)

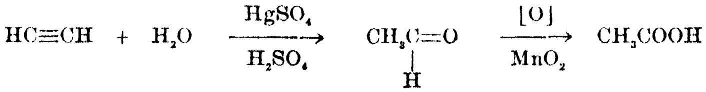
Large quantities of formic acid were formerly shipped to the East Indies where the compound was used to coagulate the collected sap of rubber trees as a step in the preparation of rubber latex.

Acetic Acid, CH_3COOH.—Acetic acid, also known as ethanoic acid, gives vinegar its characteristic properties. The formation of acetic acid from fruit juices has been known for centuries. Acetic acid as vinegar is still made by storing fruit juices, such as cider, and allowing them to ferment. Yeasts normally are present on the fruit and in the air. These yeasts contain an enzyme, zymase, that converts the sugar in the juice to ethyl alcohol. Then other microorganisms, particularly ***Bacterium aceti*** and *Mycoderma aceti,* convert the ethyl alcohol to acetic acid. These microorganisms derive energy for their life processes from the oxidation of ethyl alcohol.

Other substances used for the manufacture of vinegar are molasses and corn starch. Enzymes convert the sugar in these substances to ethyl alcohol, which is oxidized to acetic acid by various methods.

Closely related to the natural, but slow, process of fermentation is the commercial method of producing vinegar, known as the quick vinegar process. Wooden vats are filled with curly beechwood shavings, which do not pack. The shavings are inoculated by pouring a suspension of *Mycoderma aceti* and *Bacterium aceti* (mother of vinegar) over them. The purpose of the shavings is to present a large surface for the oxidation reaction. Dilute solutions of alcohol are allowed to trickle slowly over the shavings. A plentiful supply of oxygen is secured by forcing air into the vats through openings at the bottom and the sides. The process is repeated several times, the temperature being maintained at about 30° to 35° C. The process requires from eight to fourteen days and yields a product containing from 4 to 6 per cent acetic acid. This material is purified by redistillation, and the product is the familiar ''white vinegar'' available in any grocery store. Cider, malt, and wine vinegars differ from white vinegar in that they are made by the fermentation of natural products, and contain in addition to acetic acid, small amounts of other substances that impart distinctive flavors to each kind of vinegar.

The acetic acid produced by the quick vinegar process is not used for the production of the concentrated acetic acid required in industry, because evaporating such large quantities of water to obtain a concentrated product would be expensive. Nearly all of the enormous quantities of acetic acid used in industrial processes, such as the manufacture of rayon, are made from acetylene. Acetylene reacts with water in the presence of mercury salts and dilute sulfuric acid to give acetaldehyde. The acetaldehyde is then oxidized to acetic acid by passing mixtures of it and air over a manganese dioxide catalyst.



$$HC\equiv CH + H_2O \xrightarrow[H_2SO_4]{HgSO_4} \underset{\substack{|\\ H}}{CH_3C{=}O} \xrightarrow[MnO_2]{[O]} CH_3COOH$$

Acetylene Acetaldehyde Acetic acid

Another source of concentrated acetic acid is the distillate of hard wood, which, as stated previously, contains a crude product called pyroligneous acid. Formerly the pyroligneous acid was neutralized with lime (calcium hydroxide) to give "gray" or "brown" acetate of lime, depending on the amount of tarry material present. The acetate of lime then was mixed with dilute sulfuric acid, and the acetic acid was separated by fractional distillation. This separation was possible because the boiling point of sulfuric acid (290° C.) is so much higher than that of acetic acid (118° C.).

The older calcium acetate method is being supplanted by extraction with solvents, such as diethyl ether and isopropyl ether. Acetic acid and other organic substances present in the pyroligneous acid are much more soluble in the organic solvents than they are in water, so that the acetic acid is withdrawn from the aqueous solution by the organic solvent. Furthermore, the solvents form two layers when in contact with water, since they do not mix with the water. This makes the separation of the two layers easy. The low boiling ethers are easily distilled off, leaving the acetic acid and other organic substances. The acetic acid then is separated by fractional distillation.

Acid of 99.5 per cent purity can be obtained by this process and by the acetylene process. Acetic acid of this purity solidifies at 17° C., forming a slush of water-clear crystals resembling ice; and because of this characteristic, the concentrated acid usually is called *glacial* acetic acid.

Glacial acetic acid is corrosive to the skin. It does not begin to burn at once, as do inorganic acids, but when it finally is noticed and washed off with water, the acid already has eaten into the flesh. Dilute solutions of acetic acid do not show this corrosive property.

Acetic acid is a liquid with a pungent odor. It is miscible with water in all proportions. Relatively strong oxidizing agents, such as potassium permanganate and chromic acid, do not affect it; therefore, oxidation of other organic compounds often is carried out in acetic acid as a solvent.

Uses. The acid in the form of vinegar finds multiple uses in the kitchen as a condiment as in salad dressings, and in all kinds of pickles—dill pickles, mustard pickles, pickled beets, etc.

Since acetic acid is a relatively inexpensive chemical that has been produced for a long time, it has found a variety of industrial uses.

1. Acetic acid is used in the production of cellulose acetate, which is used for making noninflammable motion picture film and one type of rayon.

2. The aluminum, iron, and chromium salts of acetic acid are used as mordants in the textile industry. Mordants are substances that are applied to fabrics to enable them to adsorb certain dyes that otherwise would not combine with the fiber.

3. The double salt of copper acetate and copper arsenite is called Paris green; this salt is used as an insecticide.

4. Sugar of lead, or lead acetate, is useful in the treatment of poison ivy dermatitis.

5. The manufacture of acetone consumes considerable quantities of acetic acid.

6. Acetic acid is the basic compound for a number of organic syntheses, some of which are of great technical importance.

Propionic Acid, CH_3CH_2COOH.—Small quantities of propionic acid are present in pyroligneous acid. Propionic acid can be prepared by the oxidation of n-propyl alcohol, or by the hydrolysis of ethyl cyanide. Its properties closely resemble those of acetic acid, except that it is a slightly weaker acid. It is formed by bacteria in the ripening of Swiss and some other kinds of cheese, which fact may be partially responsible for their flavors. One of its salts, calcium propionate, sometimes is added to bread dough to inhibit the growth of molds.

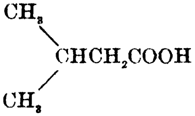
Butyric Acid, $CH_3CH_2CH_2COOH$.—Butyric acid exists in two isomeric forms. The n-butyric acid, $CH_3CH_2CH_2COOH$, occurs in the combined form as the glycerol ester in butter to the extent of 2 to 3 per cent. Butyric acid has a foul and putrid odor. The presence of small amounts of the free acid are responsible for the odor of rancid butter. It also occurs in the free state in perspiration, and as one of the products of various fermentation and decaying processes. The calcium salt of n-butyric acid is unusual due to its property of being more soluble in cold than in hot water.

Isobutyric acid, or methyl propanoic acid, $(CH_3)_2CHCOOH$, is similar to n-butyric acid in most of its properties, except that it is more easily oxidized and is not miscible with water.

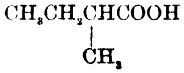
Valeric Acid.—The five-carbon homologue of the fatty acid series occurs in four isomeric forms:

n-Valeric acid: $CH_3CH_2CH_2CH_2COOH$

Isovaleric or 3-methyl butanoic acid:

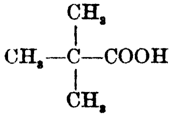


Active valeric or 2-methyl butanoic acid:



$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH$

Trimethyl acetic or 2,2-dimethyl propanoic acid:



$CH_3-\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}-COOH$

The properties of the various isomers are similar, except that the more highly branched the carbon chain, the more easily the compound is oxidized. The formulas are offered to the student as an example of chain isomerism among the acids.

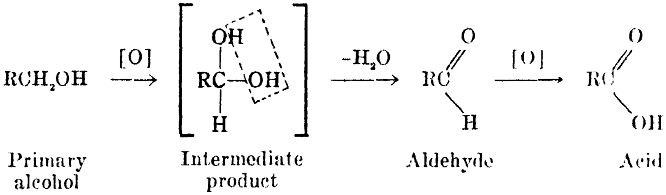
Isovaleric acid, the common form, occurs in the free state in valerian root and in animal excretions. It has an odor similar to that of butyric acid.

Higher Fatty Acids.—Only the fatty acids with an even number of carbon atoms are of much importance. Those containing four or more carbon atoms occur in combination with glycerol in animal and vegetable fats and oils, and often are termed *fat acids.* Of these, palmitic, $C_{15}H_{31}COOH$, and stearic, $C_{17}H_{35}COOH$, are the most widely distributed.

Since the higher fatty acids are mainly of interest because of their relationship to fats and oils, further discussion of them will be given in Chapter XII.

General Methods of Preparing Fatty Acids.—There are a number of general methods of preparing saturated monobasic acids.

1. Oxidation of primary alcohols and aldehydes:



2. Hydrolysis of nitriles (the nitriles, also called the alkyl cyanides, are prepared from the alkyl halides and the inorganic cyanides):

$$\underset{\substack{\text{Alkyl}\\\text{halide}}}{RX} + \underset{\substack{\text{Sodium}\\\text{cyanide}}}{NaC{\equiv}N} \rightarrow \underset{\substack{\text{Alkyl}\\\text{cyanide}}}{RC{\equiv}N} + \underset{\substack{\text{Sodium}\\\text{halide}}}{NaX}$$

The hydrolysis of the nitriles can be brought about by heating with either dilute acids or dilute alkalies:

$$\underset{\substack{\text{Alkyl}\\\text{cyanide}}}{RC{\equiv}N} + 2\,H_2O + \underset{\substack{\text{Hydrochloric}\\\text{acid}}}{HCl} \rightarrow \underset{\substack{\text{Organic}\\\text{acid}}}{RCOOH} + \underset{\substack{\text{Ammonium}\\\text{chloride}}}{NH_4Cl}$$

or

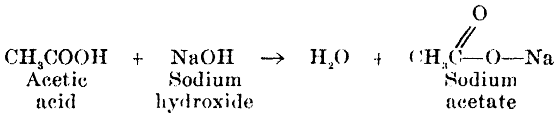
$$\underset{\substack{\text{Alkyl}\\\text{cyanide}}}{RC{\equiv}N} + H_2O + \underset{\substack{\text{Sodium}\\\text{hydroxide}}}{NaOH} \rightarrow \underset{\substack{\text{Sodium salt}\\\text{of acid}}}{RCOONa} + NH_3$$

3. Another method utilizes the Grignard reagent. Dry carbon dioxide is passed into an ethereal solution of a Grignard reagent. The addition compound formed is decomposed by passing it into a mixture of ice and dilute sulfuric acid.

$$\underset{\substack{\text{A Grignard}\\\text{reagent}}}{RMgBr} + CO_2 \rightarrow \underset{\substack{\text{Grignard addition}\\\text{compound}}}{RCO_2MgBr} \xrightarrow[H_2SO_4]{H_2O} \underset{\substack{\text{Organic}\\\text{acid}}}{RCOOH} + Mg(OH)Br$$

Acid Derivatives

Salts. Acid derivatives are those compounds in which the carboxyl group has been modified. The simplest class of such compounds is made up of the salts formed by the reaction of an organic acid and an inorganic base. Salts of organic acids differ from the acids themselves in that they are highly ionized.



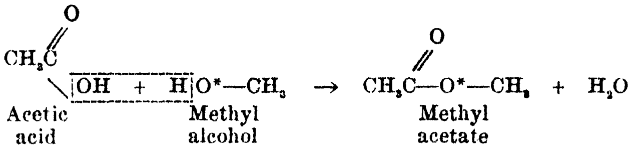
$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Sodium hydroxide}}{NaOH} \rightarrow H_2O + \underset{\text{Sodium acetate}}{CH_3C(=O)—O—Na}$$

The salt formed by the reaction of acetic acid with sodium hydroxide is a typical example of this class of acid derivative, and is a common article of commerce. Sodium acetate frequently is employed in the laboratory as a buffer. A given concentration of this salt gives a pH of known value that is not changed suddenly by addition of acid or alkali.

Recently sodium acetate has been used in large quantities as a neutralizing agent in gas masks.

Other salts of acetic acid that are of commercial importance have been discussed in connection with acetic acid. Salts of organic acids other than acetic will be discussed in connection with the uses of the various acids.

Esters.—Esters are acid derivatives that are analogous in some respects to the salts of the organic acids. They are formed from the reaction of an alcohol and either an inorganic or an organic acid. Experiments in which methyl alcohol containing heavy oxygen (atomic weight 18) reacted with an acid have demonstrated that the water formed contains ordinary oxygen (atomic weight 16) and not the isotopic form. This proves that in esterification reactions (reactions in which esters are



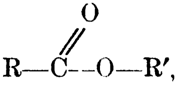
$$\underset{\text{Acetic acid}}{CH_3C(=O)—OH} + \underset{\text{Methyl alcohol}}{H—O^*—CH_3} \rightarrow \underset{\text{Methyl acetate}}{CH_3C(=O)—O^*—CH_3} + H_2O$$

---

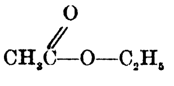
*Heavy oxygen.

formed) water is formed from the hydroxyl of the acid and the hydrogen of the alcohol, instead of the other way around.

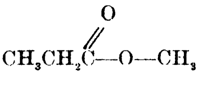
Although esters are analogous to salts in their structure, they are very different in some of their properties. The reaction by which esters are formed is not ionic, as is true in the formation of salts. Accordingly, the reaction is much slower and does not go to completion. Most esters are liquids, whereas salts are crystalline solids.

The type formula for an ester is  $R-\overset{\overset{O}{/\!/}}{C}-O-R'$, in which R and R′ may or may not be the same alkyl radical.

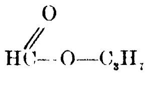
There are four esters with the molecular formula $C_4H_8O_2$. Their graphic formulas illustrate isomerism of esters.


$CH_3\overset{\overset{O}{/\!/}}{C}-O-C_2H_5$

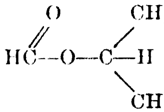
Ethyl acetate


$CH_3CH_2\overset{\overset{O}{/\!/}}{C}-O-CH_3$

Methyl propionate


$H\overset{\overset{O}{/\!/}}{C}-O-C_3H_7$

Propyl formate

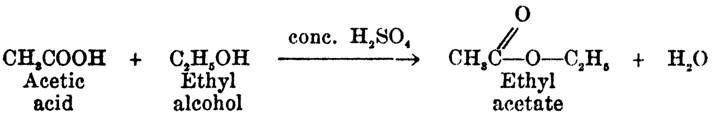

$H\overset{\overset{O}{/\!/}}{C}-O-\overset{\overset{CH_3}{/}}{\underset{\underset{CH_3}{\diagdown}}{C}}-H$

Isopropyl formate

These examples also show the system of nomenclature for esters. The name of an ester is formed from the name of the reacting alcohol and the name of the acid with an *ate* instead of an *ic* ending. For example, in the first case the ester is formed from ethyl alcohol and acetic acid, hence the name ethyl acetate. There is no commonly used International system of naming esters.

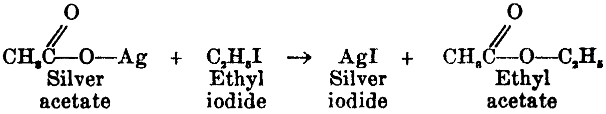
Four general methods of preparing esters will be presented, using the preparation of ethyl acetate as a particular example.

1. The reaction of an acid with an alcohol in the presence of a catalyst to take up the water formed:


$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Ethyl alcohol}}{C_2H_5OH} \xrightarrow{\text{conc. } H_2SO_4} \underset{\text{Ethyl acetate}}{CH_3\overset{\overset{O}{/\!/}}{C}-O-C_2H_5} + H_2O$$

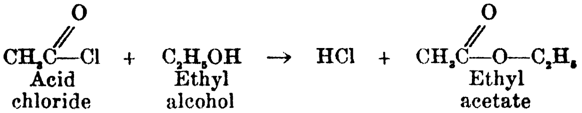
It is necessary to have some substance present to remove the water formed, otherwise the reaction reaches equilibrium when only two-thirds of the acid and alcohol have reacted.

2. The reaction of the silver salt of an organic acid and an alkyl halide:



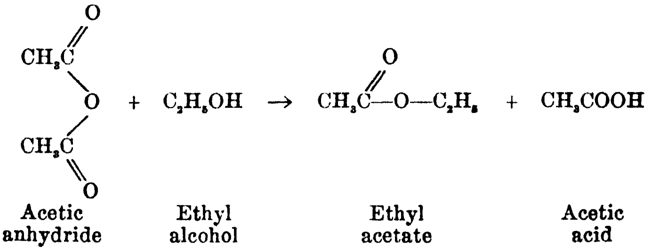
$$CH_3\overset{O}{\overset{/\!/}{C}}—O—Ag + C_2H_5I \rightarrow AgI + CH_3\overset{O}{\overset{/\!/}{C}}—O—C_2H_5$$

3. The reaction of an acid chloride with an alcohol:



$$CH_3\overset{O}{\overset{/\!/}{C}}—Cl + C_2H_5OH \rightarrow HCl + CH_3\overset{O}{\overset{/\!/}{C}}—O—C_2H_5$$

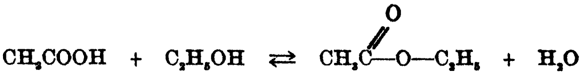
4. The reaction of an acid anhydride and an alcohol:



$$\begin{array}{l} CH_3\overset{O}{\overset{/\!/}{C}} \\ \quad\;\; \diagdown \\ \qquad O \\ \quad\;\; \diagup \\ CH_3\underset{O}{\underset{\backslash\!\backslash}{C}} \end{array} + C_2H_5OH \rightarrow CH_3\overset{O}{\overset{/\!/}{C}}—O—C_2H_5 + CH_3COOH$$

With regard to physical properties, many of the esters are substances with pleasant odors. Many of them occur in natural products and bestow the characteristic odor and flavor on essential oils, such as oil of wintergreen, and on perfumes, such as orange blossom and rose.

The most significant chemical reaction of the esters is hydrolysis. It was stated earlier that in the formation of esters, it is necessary to have some substance to take up the water formed in order for the reaction to go more nearly to completion. The reaction of acetic acid and ethyl alcohol illustrates this principle.



$$CH_3COOH + C_2H_5OH \rightleftarrows CH_3\overset{O}{\overset{/\!/}{C}}—O—C_2H_5 + H_2O$$

If we start with one mole (that is, one gram-molecular weight) of acetic acid and one mole of ethyl alcohol, at equilibrium it will be found that one-third of a mole of the acetic acid and one-third mole of the ethyl alcohol still remain unchanged. The double arrows signify that the action is reversible. The principle involved also is illustrated by the mixing of one mole of ethyl acetate and one mole of water. At equilibrium one-third of a mole of acetic acid and one-third of a mole of ethyl alcohol will be present, which is the same condition as that obtained if we start with ethyl alcohol and acetic acid. It will be seen, therefore, that the equilibrium can be reached from either direction.

These examples bring us to a discussion of equilibrium constants. Let us suppose that we have the reaction:

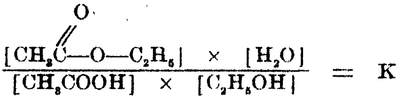
$$A + B \rightleftarrows C + D$$

The law of mass action states that the speed of a chemical reaction at a particular instant is proportional to the concentration of the reactants at that instant. As the concentration of A and B decreases, the speed of formation of C and D will decrease. The reaction in the opposite direction then will increase; that is, the reaction of C and D to form A and B will increase. At a certain point, depending on the temperature and the nature of the reacting substances, the speed of formation of C and D will equal the formation of A and B. The equilibrium point can be compared to a scale that has an equal weight on each side. At equilibrium the concentration of the substances taking part in the reaction, expressed in moles per liter, can be put in the form of an equation. The brackets around the substances indicate that its concentration is expressed as moles per liter.

$$\frac{[C] \times [D]}{[A] \times [B]} = K$$

In the equation, K equals a constant. That is, the ratio of the concentrations at a given temperature has a definite, fixed value.

The equilibrium constant expression can be used to determine the most favorable conditions for the formation of esters. As has been mentioned before, at equilibrium one-third of the acetic acid and ethyl alcohol originally present remain unchanged. If we start with one mole of each of these substances, then the conditions at equilibrium can be expressed as follows:



$$\frac{[CH_3\overset{\overset{O}{/\!/}}{C}\text{—}O\text{—}C_2H_5] \times [H_2O]}{[CH_3COOH] \times [C_2H_5OH]} = K$$

Substituting the actual concentrations of these substances at equilibrium:

$$\frac{[0.66] \times [0.66]}{[0.33] \times [0.33]} = K = 4$$

The significance of the value 4 is that, regardless of the concentration of any of the substances in the reaction, the ratio of the products to the reactants must equal 4. For a hypothetical case, suppose that at equilibrium (in the reaction of acetic acid and ethyl alcohol to form ethyl acetate) the concentration of the substances can be represented by the following numerical values:

$$\frac{[8] \times [4]}{[4] \times [2]} = \frac{[32]}{[8]} = 4$$

Now, if the amount of water is decreased by the use of a dehydrating agent, the condition after the action of the dehydrating agent can be represented as:

$$\frac{[16] \times [2]}{[4] \times [2]} = \frac{[32]}{[8]} = 4$$

If the water is decreased by one-half, the amount of ester must be doubled, since the value of K does not change. This is the reason that the addition of sulfuric acid or some such dehydrating agent insures that more ester will be formed.

In the hydrolysis of an ester the reverse conditions exist. It is advantageous to remove either the acid or the alcohol formed by the reaction. Sodium hydroxide is used because it reacts with acetic acid to form sodium acetate, thus removing the acetic acid from the reaction. For this reason, alkalies are used in the hydrolysis of fats, which are esters of high molecular weight acids and glycerol. The salts of the high molecular weight fatty acids are soaps. The term *saponification* is applied to the hydrolysis of all esters with alkalies, whether the salt formed is a soap or not.

Specific Esters and Their Uses.—*Methyl formate,* $HCOOCH_3$, has the lowest molecular weight of the simple esters. Because formic acid is a relatively strong acid, no catalyst is required for the formation of methyl formate. Formic acid and methyl alcohol are heated together, and the reaction proceeds nearly to completion, because the methyl formate has a low boiling point (32° C.) and distills out of the reacting mixture.

Methyl formate is used to control insects in grain and other food products.

Ethyl formate, $HCOOC_2H_5$, is a component of artificial rum.

Ethyl acetate, $CH_3COOC_2H_5$, is a water-clear liquid, almost insoluble in water, but miscible in all proportions with alcohol and ether. It is employed in industry as a solvent for cellulose nitrate lacquers, such as those used for automobile finishes. Industrial processes using cellulose acetate also utilize ethyl acetate as a solvent.

Butyl acetate, $CH_3COOC_4H_9$. Normal butyl acetate is manufactured from n-butyl alcohol and acetic acid, using sulfuric acid as a catalyst. Solvents for the nitrocellulose types of lacquer, such as Duco, usually are composed of several substances in order to give special properties, such as gloss and quick-drying, to the lacquer. The major portion of these solvents for cellulose lacquers is butyl acetate.

Amyl acetate, $CH_3COOC_5H_{11}$. Amyl acetate sometimes is known as banana oil because of its odor. It is a component of the solvents for cellulose nitrate lacquers.

Methyl butyrate, $C_3H_7COOCH_3$, is used in artificial fruit essences. This ester has the pleasant odor common to most esters. Its odor is all the more striking because the reaction of a poisonous alcohol with a foul smelling acid yields an ester used in perfumes.

Ethyl butyrate, $C_3H_7COOC_2H_5$, has the odor of pineapples.

Octyl acetate, $CH_3COOC_8H_{17}$, occurs in oranges.

Vinyl acetate, $CH_3COOCH{=}CH_2$, is used in the manufacture of synthetic resins.

Esters of the inorganic acids. The alkyl halides discussed in Chapter IV are the esters of the halogen acids and will not be discussed in this section.

The esters of the oxygen-containing inorganic acids are important in medicine, industry, and in chemical syntheses.

Ethyl nitrite, C_2H_5ONO, is formed by the reaction of nitrous acid and ethyl alcohol.

$$\underset{\substack{\text{Ethyl}\\\text{alcohol}}}{C_2H_5O}\boxed{H \; + \; HO}\underset{\substack{\text{Nitrous}\\\text{acid}}}{NO} \;\rightarrow\; \underset{\substack{\text{Ethyl}\\\text{nitrite}}}{C_2H_5O{-}N{=}O} \; + \; H_2O$$

Ethyl nitrite has an applelike odor, and its alcoholic solution is sold as sweet spirit of nitre (spirit of ethyl nitrite) for medicinal use.

Amyl nitrite, $C_5H_{11}ONO$, can be prepared by the same type of reaction as that used for ethyl nitrite. It is employed for the relief of the pain of angina pectoris and gall bladder colic.

Glyceryl trinitrate belongs to this group of compounds, but its use as an explosive has been discussed in connection with the trihydroxy alcohols (see page 168).

Dimethyl sulfate, $(CH_3)_2SO_4$, is prepared by the following reactions:

1. The reaction of methyl alcohol with sulfuric acid.

$$\underset{\text{Methyl alcohol}}{CH_3OH} + \underset{\text{Sulfuric acid}}{H_2SO_4} \rightarrow \underset{\text{Methyl hydrogen sulfate}}{CH_3{-}O{-}SO_2OH} + H_2O$$

2. The distillation of methyl hydrogen sulfate under diminished pressure yields dimethyl sulfate.

$$\underset{\text{Methyl hydrogen sulfate}}{2\,CH_3{-}O{-}SO_2OH} \rightarrow H_2SO_4 + \underset{\text{Dimethyl sulfate}}{(CH_3)_2SO_4}$$

Dimethyl sulfate is inexpensive and is employed extensively as a methylating agent. It is poisonous and should be handled with extreme caution.

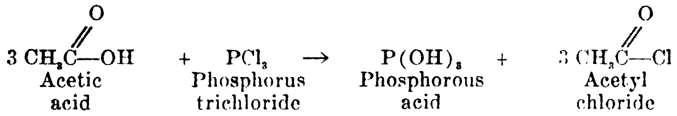
Diethyl sulfate, $(C_2H_5)_2SO_4$, is used as an ethylating agent. It has a peppermint-like odor, and, unlike dimethyl sulfate, is nontoxic.

Acyl Halides.—Another class of acid derivatives is known as acyl halides. The compounds of this class are formed by the replacement of the OH group in the acid by a halogen; consequently, the type formula for this class of compounds is RCOX, where X is chlorine, bromine, or iodine. The most common class is the acyl chlorides. This is true because they are less expensive and are easier to produce than the other halides. The acyl chlorides, or acid chlorides as they sometimes are called, are the only ones that we shall discuss in this section. The acyl group of an acid is the part of the acid molecule remaining after the hydroxyl group has been removed. Therefore, the type formula for an acyl radical is RCO—. The student should not confuse the acyl radical with the acid radical, RCOO—, formed in ionization. The name of the acyl radical of an acid is obtained by dropping the *ic* in the name of the acid, and adding *yl* (i.e., acet*yl* from acet*ic*). The systematic name for the acyl halides is obtained by dropping the *e* of the hydrocarbon name, and adding *oyl;* for example, $CH_3\overset{\overset{O}{/\!/}}{C}\text{—}Cl$ by this system is called ethanoyl chloride.

The acid chlorides are more reactive than the acids themselves. In fact, the acid chloride of formic acid is too reactive to exist at ordinary temperatures; hence, the first *stable* acid chloride contains two carbon atoms.

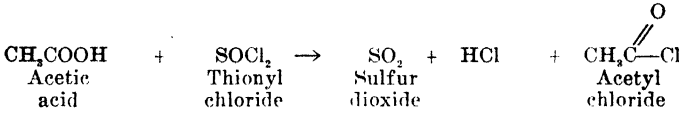
General methods of preparing acid (acyl) chlorides are illustrated by the methods for the preparation of acetyl chloride.

1. Reaction of acetic acid with phosphorus trichloride:



$$\underset{\text{Acetic acid}}{3\,CH_3\overset{\overset{O}{/\!/}}{C}\text{—}OH} + \underset{\text{Phosphorus trichloride}}{PCl_3} \rightarrow \underset{\text{Phosphorous acid}}{P(OH)_3} + \underset{\text{Acetyl chloride}}{3\,CH_3\overset{\overset{O}{/\!/}}{C}\text{—}Cl}$$

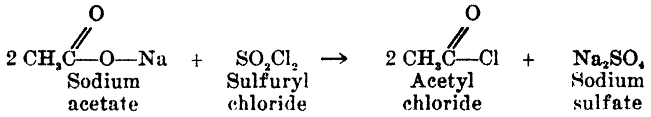
2. A widely used laboratory method is by the reaction of an acid and thionyl chloride:



$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Thionyl chloride}}{SOCl_2} \rightarrow \underset{\text{Sulfur dioxide}}{SO_2} + HCl + \underset{\text{Acetyl chloride}}{CH_3\overset{\overset{O}{/\!/}}{C}\text{—}Cl}$$

This method has the great advantage that products other than the acid chloride formed in the reaction are gases, which makes it easy to purify the acid chloride.

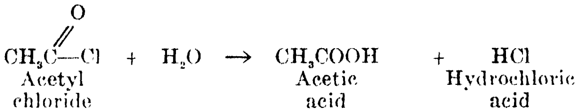
3. An important commercial method of preparation is the reaction of sodium acetate and sulfuryl chloride:



$$\underset{\text{Sodium acetate}}{2\,CH_3\overset{\overset{O}{/\!/}}{C}\text{—}O\text{—}Na} + \underset{\text{Sulfuryl chloride}}{SO_2Cl_2} \rightarrow \underset{\text{Acetyl chloride}}{2\,CH_3\overset{\overset{O}{/\!/}}{C}\text{—}Cl} + \underset{\text{Sodium sulfate}}{Na_2SO_4}$$

Reactions of acid chlorides. **The halogen atom in acyl halides is more reactive than it is in alkyl halides.**

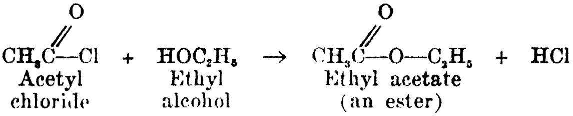
1. Reaction with water: The acid chlorides react with water to form an organic acid and hydrochloric acid. In the case of the lower members, this reaction can be violent since heat is generated.



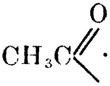
$$\underset{\text{Acetyl chloride}}{CH_3\overset{O}{\overset{\|}{C}}-Cl} + H_2O \rightarrow \underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Hydrochloric acid}}{HCl}$$

This equation explains why the vapors of acetyl chloride are irritating to the eyes and mucous membranes. Even small concentrations cause a copious flow of tears. The acid chloride reacts with the moisture in the eyes to form hydrochloric acid, which causes the irritation.

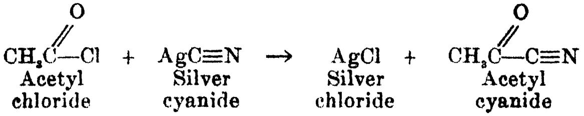
2. Acid chlorides react with the hydrogen in the hydroxyl group of the alcohols to give acetyl derivatives (esters):



$$\underset{\text{Acetyl chloride}}{CH_3\overset{O}{\overset{\|}{C}}-Cl} + \underset{\text{Ethyl alcohol}}{HOC_2H_5} \rightarrow \underset{\text{Ethyl acetate (an ester)}}{CH_3\overset{O}{\overset{\|}{C}}-O-C_2H_5} + HCl$$

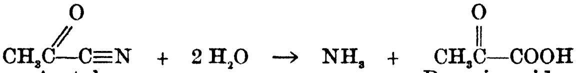
This reaction is useful in the qualitative and quantitative identification of unknown organic compounds. If an hydroxyl group is present in an unknown compound, there will be a reaction with acetyl chloride, usually with the formation of a solid acetyl derivative. Under carefully controlled conditions a quantitative determination of the number of hydroxyl groups can be made by a titration of the acetic acid formed on the hydrolysis of the acetyl derivative. Since the acetyl group occurs in so many organic derivatives, the student should drill himself until the word instantly brings to mind the grouping  $CH_3\overset{O}{\overset{\|}{C}}\diagdown$.

3. Another reaction of importance in synthetic organic chemistry is the reaction of an acid chloride with silver cyanide to form acyl cyanides.



$$\underset{\text{Acetyl chloride}}{CH_3\overset{O}{\overset{\|}{C}}-Cl} + \underset{\text{Silver cyanide}}{AgC{\equiv}N} \rightarrow \underset{\text{Silver chloride}}{AgCl} + \underset{\text{Acetyl cyanide}}{CH_3\overset{O}{\overset{\|}{C}}-C{\equiv}N}$$

As has been emphasized earlier, the nitrile group is a potential carboxyl group, and the acyl cyanides in water give α-keto acids.



$$CH_3\overset{O}{\overset{/\!/}{C}}—C{\equiv}N + 2\,H_2O \rightarrow NH_3 + CH_3\overset{O}{\overset{\|}{C}}—COOH$$

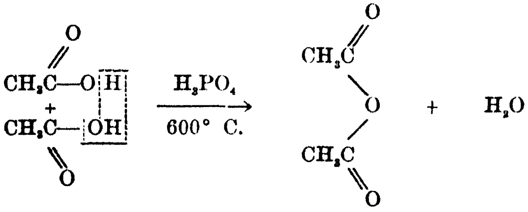
Acetyl cyanide
Pyruvic acid or α-ketopropionic acid

The acid chlorides also react with the salts of organic acids to give acid anhydrides. Acid chlorides react with ammonia to yield acid amides.

The acid chlorides of organic acids with high molecular weights can be made by the same methods as those outlined for acetyl chloride. Since the acid chlorides are reduced more easily to the corresponding aldehydes than are the acids themselves, some of the chlorides with high molecular weight acid are used for this purpose.

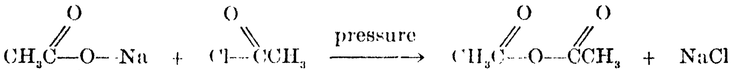
Acid Anhydrides.—Another type of acid derivative is formed by the elimination of a molecule of water between the hydroxyl groups of two acids. The type formula for acid anhydrides is R—COOOC—R. There are no commonly used I.U.C. names for the acid anhydrides; instead, they are named according to the acids from which they are derived. The anhydride of formic acid is not known, so that the simplest acid anhydride is that formed from two molecules of acetic acid.

1. Acetic anhydride can be prepared by passing the vapors of acetic acid, heated to 600° C., over a dehydrating substance, such as phosphoric acid adsorbed on charcoal. This reaction shows the structural relationship of the anhydrides to the acids.



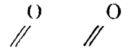
Acetic acid vapors
Acetic anhydride

2. Acetic anhydride also can be prepared by heating anhydrous sodium acetate and acetyl chloride under pressure.



$$\underset{\substack{\text{Sodium}\\ \text{acetate}}}{CH_3\overset{O}{\overset{/\!/}{C}}-O-Na} + \underset{\substack{\text{Acetyl}\\ \text{chloride}}}{Cl-\overset{O}{\overset{\backslash\!\backslash}{C}}CH_3} \xrightarrow{\text{pressure}} \underset{\substack{\text{Acetic}\\ \text{anhydride}}}{CH_3\overset{O}{\overset{/\!/}{C}}-O-\overset{O}{\overset{/\!/}{C}}CH_3} + \underset{\substack{\text{Sodium}\\ \text{chloride}}}{NaCl}$$

3. A commercial method of obtaining acetic anhydride is by the reaction of an unsaturated compound, ketene, and glacial acetic acid.

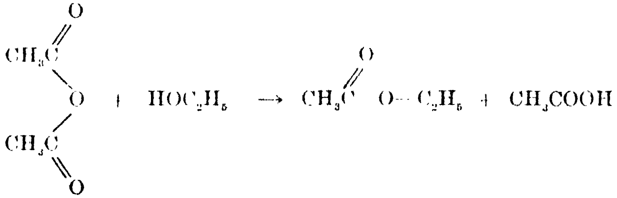


$$\underset{\text{Ketene}}{CH_2{=}C{=}O} + \underset{\text{Acetic acid}}{H_3CCOOH} \rightarrow \underset{\text{Acetic anhydride}}{CH_3\overset{O}{\overset{/\!/}{C}}-O-\overset{O}{\overset{/\!/}{C}}CH_3}$$

Acetic anhydride is typical in its chemical reactions of the entire class of acid anhydrides. Similar anhydrides of other acids are known, as well as mixed anhydrides formed from two unlike acids.

Acetic anhydride is a liquid with a boiling point of 140° C. and with an odor resembling glacial acetic acid. It will react with water, but the reaction is very much slower than the corresponding reaction of acetyl chloride and water. The reaction of acetic anhydride and water yields two molecules of acetic acid; this is the reverse of the reaction used for its formation.

A similar type of reaction takes place with alcohols.



$$\underset{\substack{\text{Acetic}\\ \text{anhydride}}}{(CH_3CO)_2O} + \underset{\substack{\text{Ethyl}\\ \text{alcohol}}}{HOC_2H_5} \rightarrow \underset{\substack{\text{Ethyl}\\ \text{acetate}}}{CH_3\overset{O}{\overset{/\!/}{C}}-O-C_2H_5} + \underset{\substack{\text{Acetic}\\ \text{acid}}}{CH_3COOH}$$

This reaction between acetic anhydride and the hydrogen of the hydroxyl group of another organic compound is important both commercially and in the laboratory for the introduction of the acetyl group ($CH_3C\!\overset{O}{<}$). Commercially, acetic anhydride, in the presence of a small amount of sulfuric acid, is used in the formation of acetyl derivatives of cellulose. This yields cellulose acetate, which is employed in the manufacture of movie film, plastics, and acetate rayon. As we shall see later, cellulose is a high molecular weight compound that contains hydroxyl groups.

In the laboratory, acetic anhydride yields acetyl derivatives of hydroxyl compounds. These derivatives usually are crystalline solids with definite melting points, and are useful in the identification of unknown hydroxyl compounds. In this respect, the use of acetic anhydride is similar to that of acetyl chloride.

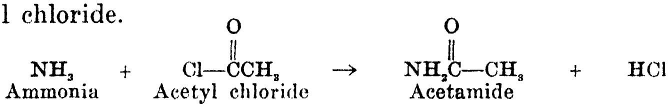
The reaction between acid anhydrides and ammonia yields acid amides.

The production of acetic anhydride in the United States increased from 256 million pounds in 1940 to 522 million pounds in 1946.

Acid Amides.—Acid derivatives in which the hydroxyl of the carboxyl group has been replaced by an amine (—NH_2) group are known as acid amides. The type formula for acid amides is $RCONH_2$. There is no commonly used International system of naming the amides; their names are derived from the name of the acid (formamide, acetamide, etc.).

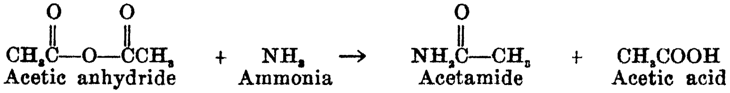
The amide of formic acid, formamide, is known, but since the preparation of acetamide is a common laboratory experiment and since it has more industrial uses than other amides, we shall consider acetamide as typical of the class.

1. Acetamide can be prepared by the action of ammonia on acetyl chloride.



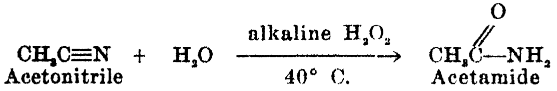
$$\underset{\text{Ammonia}}{NH_3} + \underset{\text{Acetyl chloride}}{Cl{-}\overset{O}{\overset{\|}{C}}CH_3} \rightarrow \underset{\text{Acetamide}}{NH_2\overset{O}{\overset{\|}{C}}{-}CH_3} + HCl$$

2. The reaction between acetic anhydride and ammonia also yields acetamide.



$$\underset{\text{Acetic anhydride}}{CH_3\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}CH_3} + \underset{\text{Ammonia}}{NH_3} \rightarrow \underset{\text{Acetamide}}{NH_2\overset{O}{\overset{\|}{C}}{-}CH_3} + \underset{\text{Acetic acid}}{CH_3COOH}$$

3. Acetamide can be prepared by the partial hydrolysis of methyl cyanide (acetonitrile) by means of concentrated sulfuric acid or alkaline hydrogen peroxide.

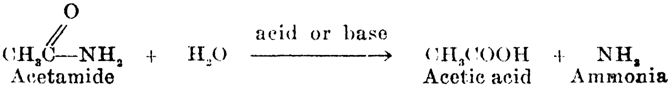


$$\underset{\text{Acetonitrile}}{CH_3C{\equiv}N} + H_2O \xrightarrow[\text{40° C.}]{\text{alkaline } H_2O_2} \underset{\text{Acetamide}}{CH_3\overset{O}{\overset{/\!/}{C}}{-}NH_2}$$

There are more convenient methods of preparing acetamide in the laboratory, but this reaction is presented to emphasize to the student the intermediate role of amides in the preparation of acids by the hydrolysis of nitriles. Amides are hydrolyzed to give acids.

Acetamide is a crystalline solid with an odor resembling that of mice. This odor is due to traces of impurities in the acetamide. It usually is purified by distillation, but since it boils at 220° C., an air instead of a water condenser must be used or the acetamide will solidify and clog the condenser. The compound is soluble in water, alcohol, and ether.

The most typical reaction of the acid amides is hydrolysis. Acetamide is easily hydrolyzed by boiling it with water in the presence of a small amount of acid or alkali.

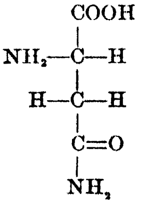


$$\underset{\text{Acetamide}}{CH_3\overset{O}{\overset{/\!/}{C}}\text{—}NH_2} + H_2O \xrightarrow{\text{acid or base}} \underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Ammonia}}{NH_3}$$

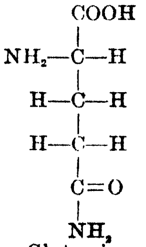
Both acids and bases hasten the reaction since they remove one or the other of the products of the reaction and hence cause the reaction to go to completion. For example, sodium hydroxide neutralizes the acid formed by the hydrolysis.

Acetamide is finding increasing use as a solvent for various types of organic compounds. The amides also are convenient starting materials for preparing amines (see page 293).

Two naturally occurring amides, asparagine and glutamine, are of great importance in the nitrogen metabolism of plants, especially in the germinating seed. The structural formulas for these two amides are:



Asparagine
(amide of aspartic acid)



Glutamine
(amide of glutamic acid)

Study Questions

1. What is the characteristic group present in all organic acids? In what way do organic acids differ from inorganic acids? In what respect are they similar?
2. What is the general formula for the series of saturated monobasic acids?
3. In what chemical properties does formic acid differ from other acids of this homologous series? Illustrate one such difference by an equation.
4. To what commercial uses is formic acid being put?
5. What are the common name and the I.U.C. name of the characteristic acid of vinegar?
6. Describe in some detail the quick vinegar process.
7. What is glacial acetic acid? From what property did the substance derive this name?
8. What are some of the uses of acetic acid?
9. What acid is responsible for the odor of rancid butter?
10. Write an equation to represent the formation of the potassium salt of butyric acid.
11. What are esters? What is the type formula for an ester?
12. What is meant by an equilibrium constant? Of what significance is it in esterification reactions?
13. Write an equation illustrating a general method of preparing esters.
14. What physical property is common to most esters?
15. How do the acyl halides differ from the alkyl halides? How does the acyl radical differ from the carboxyl radical?
16. What is the acetyl radical? How can acetyl chloride be used in quantitative determinations of the number of hydroxyl groups present in an unknown compound?
17. What is the type formula for acid anhydrides? Write an equation to represent the formation of acetic anhydride.

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CHAPTER X

DIBASIC ACIDS

Introduction.—Organic acids that have two replaceable hydrogen atoms per molecule are called dibasic or dicarboxylic acids. These acids are found to a greater extent in nature than are the saturated monocarboxylic acids. Since they contain two reactive hydrogens, they are capable of forming two series of salts: the acid salts, in which only one of the hydrogens is replaced by a metal; and the normal salts, in which both hydrogens have been substituted. The first five members of the series are listed in Table XI.

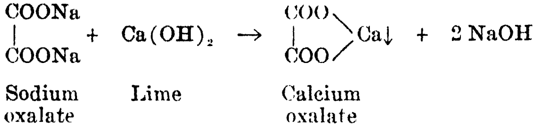
TABLE XI

FORMULAS AND MELTING POINTS OF SOME SATURATED DIBASIC ACIDS

NAME	FORMULA	MELTING POINT, ° C.
Oxalic	$\mathrm{HOOC{-}COOH}$	101
Malonic	$\mathrm{HOOC{-}CH_2{-}COOH}$	136
Succinic	$\mathrm{HOOC{-}(CH_2)_2{-}COOH}$	185
Glutaric	$\mathrm{HOOC{-}(CH_2)_3{-}COOH}$	98
Adipic	$\mathrm{HOOC{-}(CH_2)_4{-}COOH}$	153

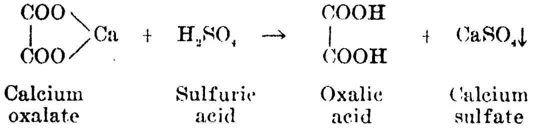
Oxalic Acid, $(COOH)_2$.—Oxalic acid is the first member of an homologous series of saturated dibasic acids. It occurs rather extensively in the vegetable kingdom, especially as the salt of potassium or calcium in certain plants, such as sorrel (of the *oxalis* family) and rhubarb.

The acid formerly was prepared commercially by fusing sawdust or shavings, preferably from soft wood, with sodium or potassium hydroxide at a temperature of 240° C. Two parts of alkali are used to one part of wood for the reaction. The mixture is extracted with hot water, and the sparingly soluble sodium or potassium oxalate crystallizes out on cooling. By treatment with lime (calcium hydroxide) insoluble calcium oxalate is formed. Oxalic acid is obtained from the calcium oxalate by treatment with sulfuric acid.



$$\begin{array}{l}COONa\\|\\COONa\end{array} + Ca(OH)_2 \rightarrow \begin{array}{l}COO\diagdown\\|\qquad\;\; Ca\downarrow\\COO\diagup\end{array} + 2\,NaOH$$

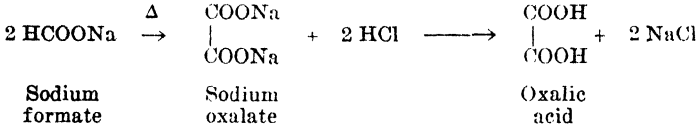
Sodium oxalate · Lime · Calcium oxalate



$$\begin{array}{l}COO\diagdown\\|\qquad\;\; Ca\\COO\diagup\end{array} + H_2SO_4 \rightarrow \begin{array}{l}COOH\\|\\COOH\end{array} + CaSO_4\downarrow$$

Calcium oxalate · Sulfuric acid · Oxalic acid · Calcium sulfate

A widely used commercial method of preparing the acid is to heat sodium formate. Sodium oxalate, from which the oxalic acid can be obtained by treatment with an acid, is the product of this reaction.

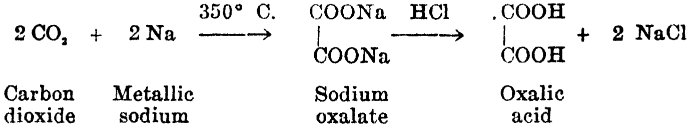


$$2\,HCOONa \xrightarrow{\Delta} \begin{array}{l}COONa\\|\\COONa\end{array} + 2\,HCl \longrightarrow \begin{array}{l}COOH\\|\\COOH\end{array} + 2\,NaCl$$

Sodium formate · Sodium oxalate · Oxalic acid

Carbohydrates, such as sugar and starch, yield oxalic acid when they are warmed with concentrated nitric acid.

Oxalic acid can be made by the action of carbon dioxide on sodium at 350° C.



$$2\,CO_2 + 2\,Na \xrightarrow{350^\circ\ C.} \begin{array}{l}COONa\\|\\COONa\end{array} \xrightarrow{HCl} \begin{array}{l}COOH\\|\\COOH\end{array} + 2\,NaCl$$

Carbon dioxide · Metallic sodium · Sodium oxalate · Oxalic acid

Properties. The oxalic acid that crystallizes from water contains two molecules of water of hydration. From an acid solution, however, it crystallizes in the anhydrous form. The hydrated acid melts at 101° C., and the anhydrous form melts at a higher temperature, 189° C.

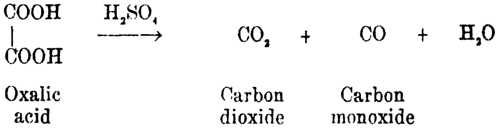
Oxalic acid is a much stronger acid than any of its homologues. In fact, in dilute solution (0.05 N), oxalic acid is as strong as the same concentration of sulfuric acid. Unlike the other members of the homologous series, oxalic acid has no alkyl chain;

therefore, some of its reactions are unlike those of the other members of the series. It is easily oxidized to carbon dioxide and water by potassium permanganate in acid solution.

$$\underset{\text{Oxalic acid}}{5\,(COOH)_2} + \underset{\text{Potassium permanganate}}{2\,KMnO_4} + \underset{\text{Sulfuric acid}}{3\,H_2SO_4} \rightarrow \underset{\text{Potassium sulfate}}{K_2SO_4} + \underset{\text{Manganese sulfate}}{2\,MnSO_4} + 10\,CO_2 + 8\,H_2O$$

This type of reaction is used in analytical chemistry for standardizing oxidizing solutions. If the quantity of oxalic acid or one of its salts is weighed carefully, the amount of oxidizing substance present in the solution can be determined.

If the acid is heated in the presence of sulfuric acid, carbon monoxide, carbon dioxide, and water are formed.



$$\underset{\text{Oxalic acid}}{\begin{matrix}COOH\\ |\\ COOH\end{matrix}} \xrightarrow{H_2SO_4} \underset{\text{Carbon dioxide}}{CO_2} + \underset{\text{Carbon monoxide}}{CO} + H_2O$$

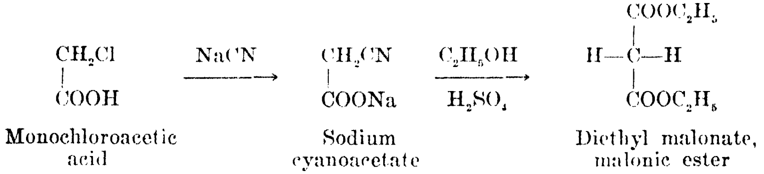
The calcium salt of oxalic acid is a very insoluble compound. This property is utilized in the quantitative procedure for the determination of calcium. Since sodium and ammonium oxalates are more soluble than oxalic acid itself, solutions of these salts are added to the solution containing the calcium compound. The insoluble calcium oxalate that forms is separated by filtration, and then is heated to convert it to calcium oxide. The calcium oxide is weighed on a sensitive balance. From the amount obtained, the weight of calcium in the sample can be calculated.

Oxalic acid taken internally in any quantity is poisonous. The antidote is milk of lime, milk, or any other good source of calcium. The toxic oxalic acid is rendered inert by the formation of the extremely insoluble calcium oxalate. The magnesium salt of oxalic acid is almost as insoluble as the calcium salt, and milk of magnesia (which contains magnesium hydroxide) also is effective as an antidote for oxalic acid poisoning.

Because oxalic acid is a strong reducing agent, both the acid and its salts are used in dry cleaning and laundry work for removing rust and some ink stains. The insoluble ferric compounds are reduced to the more soluble ferrous salts, which can then be removed by washing.

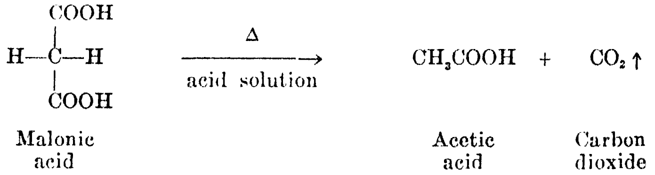
Ferrous oxalate is used as a photographic developer, and potassium ferric oxalate is used for making platinum prints in photography. The acid and its antimony salts find use as mordants in the dyeing and printing industries. Still another use of oxalic acid is as a bleach for leather, straw, and wood.

Malonic Acid, HOOC—CH$_2$—COOH.—Malonic acid occurs in sugar beets as the calcium salt. The free acid is unstable, and is of little importance. Usually the diethyl ester is synthesized instead of the acid itself. The diethyl ester of malonic acid is prepared from monochloroacetic acid and sodium cyanide by the hydrolysis of the nitrile (cyanoacetate) in the presence of ethyl alcohol.



$$\begin{matrix}CH_2Cl\\|\\COOH\end{matrix} \xrightarrow{NaCN} \begin{matrix}CH_2CN\\|\\COONa\end{matrix} \xrightarrow[H_2SO_4]{C_2H_5OH} \begin{matrix} & COOC_2H_5 & \\ & | & \\ H- & C & -H\\ & | & \\ & COOC_2H_5 & \end{matrix}$$

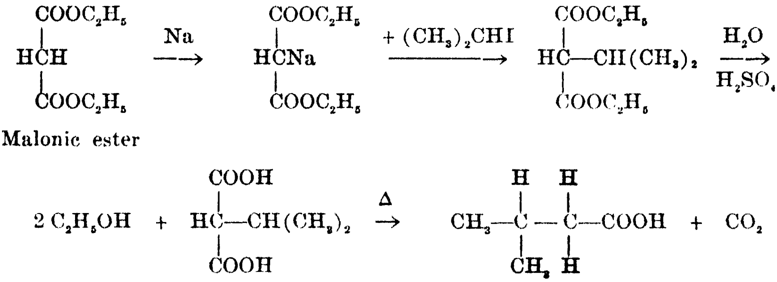
This method of preparation, rather than the formation of the acid followed by addition of the ethyl groups, is advisable. When free malonic acid is heated in acid solution, it easily loses carbon dioxide from one carboxyl group to yield acetic acid.



$$\begin{matrix} & COOH & \\ & | & \\ H- & C & -H\\ & | & \\ & COOH & \end{matrix} \xrightarrow[\text{acid solution}]{\Delta} CH_3COOH + CO_2\uparrow$$

Malonic ester is used widely in organic chemistry for what is known as the *malonic ester synthesis.* The CH$_2$ group between the two esterified carboxyl groups is known as an *active methylene* group. The hydrogens in this group react as though they were weakly acidic; that is, they can be replaced by metals such as sodium. This usually is true when a methylene group occurs between the two carbonyl oxygens of a molecule.

When one of the hydrogens of the methylene group is replaced by sodium, the resulting derivative can be made to react with an alkyl halide. The alkyl group takes the place of the sodium. If the malonic ester then is hydrolyzed to the free acid and heated, the free acid loses carbon dioxide. This yields an alkyl-substituted acetic acid.



$$\underset{\text{Malonic ester}}{\begin{array}{l}COOC_2H_5\\ |\\ HCH\\ |\\ COOC_2H_5\end{array}} \xrightarrow{Na} \begin{array}{l}COOC_2H_5\\ |\\ HCNa\\ |\\ COOC_2H_5\end{array} \xrightarrow{+\,(CH_3)_2CHI} \begin{array}{l}COOC_2H_5\\ |\\ HC{-}CH(CH_3)_2\\ |\\ COOC_2H_5\end{array} \xrightarrow[H_2SO_4]{H_2O}$$

$$2\,C_2H_5OH + \begin{array}{l}COOH\\ |\\ HC{-}CH(CH_3)_2\\ |\\ COOH\end{array} \xrightarrow{\Delta} \begin{array}{c}\quad H\quad H\\ \quad |\quad\ |\\ CH_3{-}C{-}C{-}COOH\\ \quad |\quad\ |\\ \quad CH_3\ H\end{array} + CO_2$$

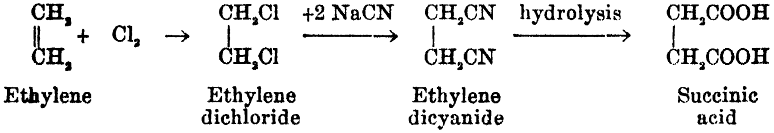
2-Methyl butyric acid,
isopropyl acetic acid

Such acids as the end product in the foregoing reaction sometimes are known as substituted acetic acids, since one of the hydrogen groups in acetic acid has been substituted by an alkyl group.

By a similar series of reactions, the other hydrogen of the methylene group in malonic ester also can be substituted. Such a series of reactions is useful in the synthesis of complex acids.

Succinic Acid, $HOOC(CH_2)_2COOH$.—Succinic acid occurs in amber, a fossil gum, and was obtained originally by distillation of this substance. The name is indicative of this fact, since the Latin term for amber is *succinum*. The acid occurs also in some kinds of brown coal, in resins, in turpentine, in normal tissues, and in the urine of animals. Small amounts of it are formed in the alcoholic fermentation of sugars.

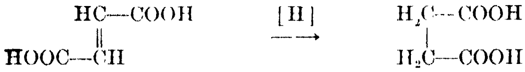
The acid can be synthesized from ethylene by hydrolysis of the corresponding dicyanide.



$$\underset{\text{Ethylene}}{\begin{array}{l}CH_2\\ \|\\ CH_2\end{array}} + Cl_2 \rightarrow \underset{\text{Ethylene dichloride}}{\begin{array}{l}CH_2Cl\\ |\\ CH_2Cl\end{array}} \xrightarrow{+2\,NaCN} \underset{\text{Ethylene dicyanide}}{\begin{array}{l}CH_2CN\\ |\\ CH_2CN\end{array}} \xrightarrow{\text{hydrolysis}} \underset{\text{Succinic acid}}{\begin{array}{l}CH_2COOH\\ |\\ CH_2COOH\end{array}}$$

In connection with this equation, the student will recall that it has been emphasized previously that cyanide (CN) groups are potential carboxyl (COOH) groups.

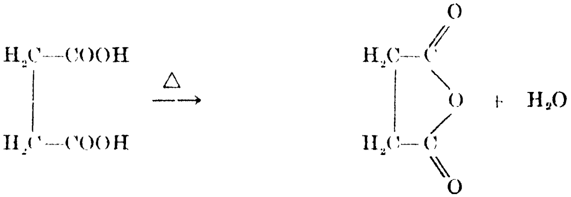
Most of the succinic acid of commerce, however, is prepared by the electrolytic reduction of fumaric acid.



$$\text{HC—COOH} \parallel \text{HOOC—CH} \xrightarrow{[H]} \text{H}_2\text{C—COOH} \mid \text{H}_2\text{C—COOH}$$

Fumaric acid Succinic acid

Succinic acid is characterized by the formation of an anhydride when it is heated alone or with a dehydrating agent, such as acetic anhydride.

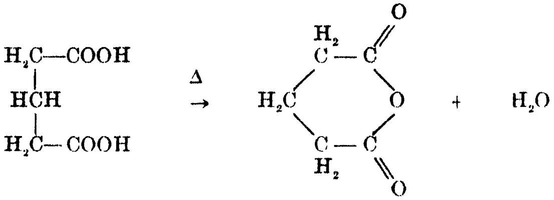


Succinic acid Succinic anhydride

When the two lower members belonging to the same homologous series as succinic acid (oxalic acid and malonic acid) are heated, they do not show this characteristic.

Succinic acid occasionally is used in medicine, and is useful in the perfume and dye industries.

Glutaric Acid, $HOOC(CH_2)_3COOH$.—The name of the saturated five-carbon dicarboxylic acid is glutaric acid. It can be prepared by the general methods already outlined for the preparation of succinic acid. Like succinic acid, when glutaric acid is heated, an anhydride is formed.



Glutaric acid Anhydride of glutaric acid

Adipic Acid, $HOOC(CH_2)_4COOH$.—The six-carbon homologue of oxalic acid is known as adipic acid. It was first obtained by the oxidation of fats (Latin: *adeps*, fat) with nitric acid. Unlike succinic and glutaric acids, adipic acid does not readily form an anhydride when it is heated. As will be seen later (Chapter XIX), ring structures containing five or six

Fig. 32.—Hanks of nylon filaments, which are many times the diameter of the fine yarn that goes into women's hosiery. This large diameter nylon is produced for surgical sutures, fishing leaders, and bristles for toothbrushes, hairbrushes, and industrial brushes. (Courtesy of the Du Pont Company.)

atoms linked together are more easily formed than rings containing a greater or smaller number of atoms. The anhydrides of succinic and glutaric acids are five- and six-membered rings. The anhydride of adipic acid contains seven atoms in the ring.

Adipic acid is much used in the manufacture of synthetic resins. It is used also as a substitute for tartaric acid in some baking powders.

The products obtained by the polymerization of polymethylene amides of such acids as adipic and sebacic ($HOOC(CH_2)_8$-$COOH$) are the substances from which synthetic nylons are formed. About 30 such fiber-forming polyamides have been synthesized. The most common type and the first produced results from the reaction between adipic acid and hexamethylenediamine. This is called the "6-6 polymer," since there are six carbon atoms in each of the reacting molecules. The end products have large molecular weights, averaging about 12,500, and have about 920 units in each chain of the polymer.

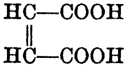
Nylon popularly is associated with its use as a textile fiber for full-fashioned hosiery. Filaments of this polyamide can be drawn out thinner than any other artificial fiber except glass. However, filaments of large diameter have been used successfully for brush bristles, surgical sutures, and tennis racket strings. Because of the extensive use of nylon in industrial brushes, American industry is no longer dependent on the importation of hog bristles from the Far East.

Unsaturated Dibasic Acids.—In addition to the saturated dicarboxylic acids, there are dicarboxylic acids that contain a double bond. The most frequently encountered members of this class of compounds are maleic and fumaric acids.

These acids, in addition to their industrial importance, are of special interest because they illustrate a new type of isomerism. Although both maleic and fumaric acids have the molecular formula $C_4H_4O_4$, they differ in their physical and chemical properties.

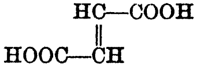
	Melting point	Solubility in 100 cc. of water at 20° C.	Anhydride formation
Fumaric acid	287° C.	0.6 g.	Does *not* form an anhydride
Maleic acid	130° C.	60.0 g.	Forms an anhydride

Largely on the basis of the fact that maleic acid forms an anhydride and that fumaric acid does not, the graphic formulas for the two acids are represented as follows:



$$\begin{array}{l}\mathrm{HC{-}COOH}\\ \|\\ \mathrm{HC{-}COOH}\end{array}$$

Maleic acid (cis isomer)



$$\begin{array}{rl} & \mathrm{HC{-}COOH}\\ & \|\\ \mathrm{HOOC{-}} & \mathrm{CH}\end{array}$$

Fumaric acid (trans isomer)

The graphic formulas show that in maleic acid the carboxyl groups are closer to each other in space than they are in fumaric acid. Hence it might be expected that water would split out more easily from these two carboxyl groups than from those groups in fumaric acid. The experimental results bear out this expectation, since only maleic acid forms an anhydride.

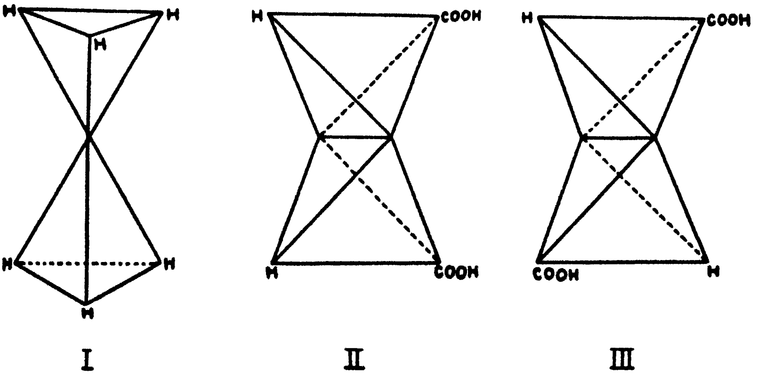


Fig. 33.—I, Tetrahedral formula for ethane, showing possibility of free rotation of the carbon atoms. II, Maleic acid. The presence of the double bond, indicated by the union of the tetrahedra along an edge, prevents free rotation of the carbon atoms and gives rise to geometric isomerism. Maleic acid is the isomer that forms an anhydride because the carboxyl groups are nearer to each other in space than they are in fumaric acid. III, Fumaric acid, the trans isomer, does not form an anhydride because the carboxyl groups are too far removed from each other in space.

Fumaric and maleic acids illustrate *geometric* or *cis-trans isomerism,* a kind of isomerism common to all ethylene derivatives. In order to understand more fully the reason for geometric isomerism, it is necessary to consider a theoretical basis for the phenomenon. It was stated earlier that many of the spatial relationships of carbon can be represented by the concept of a tetrahedral carbon atom. In this concept the four valences of the carbon atom are thought of as being directed outward toward the corners of a regular tetrahedron imagined to be circumscribed about the carbon atom as its center.

Two carbon atoms united by a single bond can be represented by tetrahedra joined through one corner of each tetrahedron. In this situation free rotation can be assumed to take place around an axis through the points of attachment of the two tetrahedra. This arrangement is represented by Fig. 33, I.

In order to represent the union of two carbon atoms by a double bond, it is necessary to join the tetrahedra at two corners, i.e., join them along an edge. When the carbon atoms are combined in this manner, the possibility of free rotation or spin is lost.

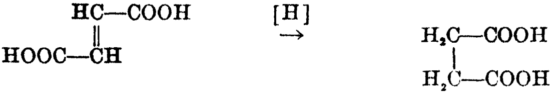
Fig. 33, II and III, shows that the carboxyl groups of maleic acid are closer to each other in space than are the carboxyl groups of fumaric acid. Since there is no possibility of free rotation, the positions of the carboxyl groups are fixed; this explains the existence of isomeric compounds with different chemical and physical characteristics.

In geometric isomerism the isomer having the two groups under consideration (the carboxyl groups in this instance) on the same side of the plane established by the double bond is known as the *cis* form. In the *trans* isomer these groups are on opposite sides, or across the plane of the double bond from each other.

A convenient aid to the student in recalling the relative positions of the groups in the two isomers is to remember that the Latin prefix *trans* means *across*. This prefix occurs in such common words as transcontinental (across the continent) and transport (carry across).

Fumaric acid. Fumaric acid occurs in nature in fungi and in such plants as Iceland moss. Commercially, it is obtained chiefly by a fermentation process.

Fumaric acid is sparingly soluble in water, from which it crystallizes as small white needles. On reduction it yields succinic acid.

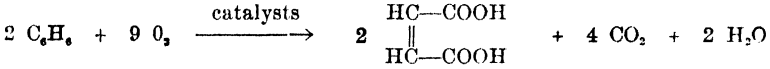


$$\begin{matrix} \text{HC—COOH} \\ \| \\ \text{HOOC—CH} \end{matrix} \xrightarrow{[H]} \begin{matrix} \text{H}_2\text{C—COOH} \\ | \\ \text{H}_2\text{C—COOH} \end{matrix}$$

Fumaric acid Succinic acid

If fumaric acid is treated with phosphorus pentachloride, it is converted to maleic anhydride, which in turn can be hydrolyzed to form maleic acid. Maleic acid is of greater commercial importance than is fumaric acid.

Maleic acid. Maleic acid does not occur in nature. As was mentioned in connection with fumaric acid, maleic acid results when fumaric acid is treated with phosphorus pentachloride. Industrially, the acid is made by the air oxidation of benzene vapor in the presence of catalysts.

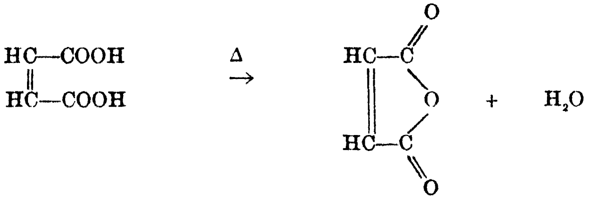


$$2\ C_6H_6 + 9\ O_2 \xrightarrow{\text{catalysts}} 2 \begin{matrix} \text{HC—COOH} \\ \| \\ \text{HC—COOH} \end{matrix} + 4\ CO_2 + 2\ H_2O$$

Benzene vapor Maleic acid

This acid is freely soluble in water, and crystallizes in the form of large plates. It is a much stronger acid than fumaric, as can be shown by a comparison of the ionization constants of the two compounds. Fumaric has an ionization constant of 0.093, while that for maleic acid is 1.17.

When the acid is heated, the anhydride is formed.



Maleic acid Maleic anhydride

Like fumaric acid, maleic acid forms succinic acid when it is reduced.

The acid is used in the preparation of ester-type compounds known as alkyd resins. Maleic anhydride resins make hard, tough, fast-drying lacquers with an excellent color retention.

Varnishes made with maleic resins show a high resistance to yellowing, and thus make whiter enamels possible. In 1946 the production of maleic acid-alkyd type resins amounted to 44,396,000 pounds.

There is some evidence to show that maleic acid retards the onset of rancidity in edible fats and oils.

Study Questions

1. Give the names of the first five members of the series of saturated dibasic acids.
2. In what respects does oxalic acid differ from its homologues?
3. Why is milk an antidote for oxalic acid poisoning?
4. How might one remove a rust stain from a piece of white cotton fabric?
5. By means of a series of equations, show how methylethyl acetic acid (α-methylbutyric acid) can be formed using the ***malonic ester synthesis.***
6. What are some natural sources of succinic acid?
7. How does succinic acid react differently when it is heated from oxalic and malonic acids?
8. Write the structural formula for glutaric anhydride.
9. Write the structural formula for adipic acid. What is the industrial importance of adipic acid and its derivatives?
10. In what respects do maleic and fumaric acids differ from each other?
11. Maleic and fumaric acids exhibit what type of isomerism?
12. What is meant by *cis* and *trans* isomers?
13. Of what industrial importance is maleic acid?

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CHAPTER XI

SUBSTITUTED ORGANIC ACIDS

Introduction.—The substituted acids are derivatives in which one or more of the hydrogens in the alkyl group of the acid have been substituted by another element or group. The number of groups that can be substituted is quite large, but we shall consider only three: the halogen, the hydroxy, and the keto groups. The halogen-substituted acids will be considered first because many of the other substituted acids can be prepared from them.

Halogen-Substituted Fatty Acids

The hydrogens in the alkyl group of an acid are similar in their reactions to the hydrogens of a hydrocarbon; consequently, as is to be expected, the hydrogens in this alkyl group can be replaced by direct halogenation. With chlorine and bromine this reaction is carried out in the presence of sunlight and catalysts, such as red phosphorus, iodine, or sulfur. Iodoacetic acid, however, is prepared by the reaction of chloroacetic acid and sodium iodide. Only the substituted acids containing the halogen on the carbon atom next to the carboxyl group, termed the alpha (α) carbon atom, can be prepared by the action of a free halogen on the acid. The chlorine-substituted acids are most commonly encountered. The halogen derivatives of formic acid have not been isolated as such, but the esters of chloroformic acid form stable compounds.

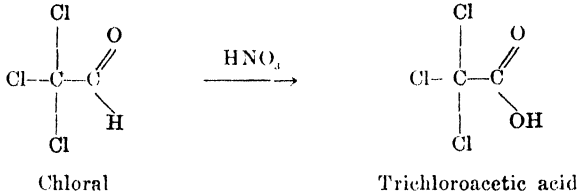
Monohalogen Substituted Acetic Acids.—When one of the hydrogens in the hydrocarbon part of acetic acid is substituted by chlorine, the compound is known as chloroacetic acid.

$$\underset{\text{Acetic acid}}{CH_3COOH} + \underset{\text{Chlorine}}{Cl_2} \xrightarrow[\text{I}_2\text{ or red phosphorus}]{\text{sunlight}} \underset{\text{Monochloroacetic acid}}{ClCH_2COOH} + \underset{\text{Hydrochloric acid}}{HCl}$$

Chloroacetic acid is used in the synthesis of indigo and malonic ester and in the preparation of glycine, an amino acid.

The new rat poison known as 1080 is monofluoroacetic acid; it is an extremely poisonous substance.

Trichloroacetic Acid, CCl_3COOH.—Trichloroacetic acid is not usually made by direct reaction with chlorine, but is prepared by the oxidation of chloral with nitric acid.

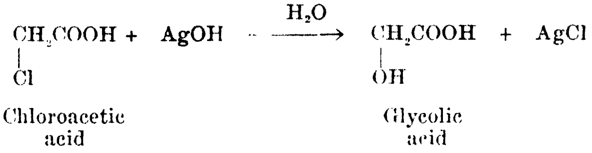


Trichloroacetic acid is a hygroscopic solid, melting at 55° C. This acid, in which all the hydrogens in the alkyl group have been replaced by chlorine, is a very much stronger acid than acetic. It is dangerously corrosive to the skin. The difference in strength of the two acids can be explained as follows. When acetic acid is dissolved in a relatively small quantity of water, only a small amount of ionization takes place: that is, the hydrogen of the carboxyl group remains largely as part of the acetic acid molecule. When the three hydrogens in the alkyl group of acetic acid are replaced by chlorine, as in trichloroacetic acid, the strongly electronegative chlorine atoms will tend to draw electrons toward themselves, and the hydrogen of the carboxyl will no longer be held so firmly by the rest of the molecule. In effect, this will cause a loosening of the H^+, and will result in the separation of the H^+ when the molecule is put into a solvent, such as water.

Trichloroacetic acid is an important reagent for the precipitation of proteins from solution. In this connection, the acid serves both as a qualitative and a quantitative reagent. The formation of a precipitate when trichloroacetic acid is added to a solution suspected of containing a protein is taken as a positive test for the presence of proteins. A 10 per cent solution of trichloroacetic acid often is used in the quantitative precipitation or removal of proteins from a solution. Trichloroacetic acid is also used for removing warts and small growths from the skin.

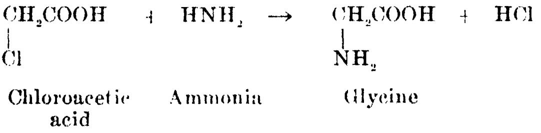
Chemical Properties of Halogen-Substituted Acids.—The halogen-substituted acids undergo three important types of reaction.

1. *Replacement with the hydroxyl group.* The halogen acids are useful in the preparation of hydroxy acids. The halogen atom is more easily replaced by the hydroxyl group than are the halogen atoms of the alkyl halides.



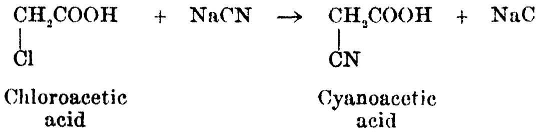
$$\underset{\text{Cl}}{\underset{|}{CH_2COOH}} + AgOH \xrightarrow{H_2O} \underset{\text{OH}}{\underset{|}{CH_2COOH}} + AgCl$$

2. *Replacement with the amino group.* With ammonia the halogen-substituted acids form amino acids.



$$\underset{\text{Cl}}{\underset{|}{CH_2COOH}} + HNH_2 \rightarrow \underset{NH_2}{\underset{|}{CH_2COOH}} + HCl$$

3. *Replacement with the cyano group.* Reaction with sodium cyanide leads to the formation of a cyano acid.



$$\underset{\text{Cl}}{\underset{|}{CH_2COOH}} + NaCN \rightarrow \underset{\text{CN}}{\underset{|}{CH_2COOH}} + NaCl$$

On hydrolysis the cyano acids yield a dibasic acid. This reaction was given as a method of preparing malonic ester, and furnishes a method of passing from monobasic acids to dibasic acids.

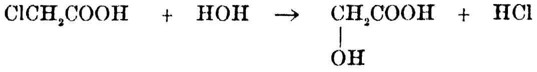
Hydroxy Acids

Just as the hydrogens in the alkyl group of acids can be substituted by halogens to give halogen-substituted acids, so can the hydrogens in the alkyl group be substituted to give hydroxy acids. It is necessary at this point to introduce a new system of nomenclature that the student will encounter in the naming of the hydroxyl acids. This system uses a Greek letter to indicate the position of the hydroxyl group with relation to the carboxyl group of the acid. The carbon atoms of the acid, beginning with the carbon atom *next to the carboxyl group,* are named by letters of the Greek alphabet. The small or lower case Greek letters, and not the capital Greek letters, which are familiar in fraternity and sorority names, are used for this purpose. The following example illustrates which carbon atom is meant by the Greek letters used in this system:

CH_3	—	CH_2	—	CH_2	—	CH_2	—	CH_2	—	COOH
ϵ		δ		γ		β		α		
epsilon		delta		gamma		beta		alpha		

Thus, there are alpha, beta, gamma, etc., hydroxy acids.

General Methods of Synthesis.—1. *Hydrolysis of the corresponding halogen acid.*

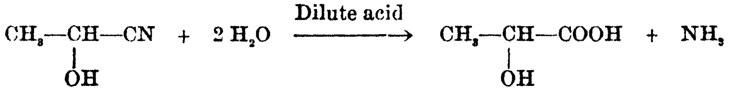


$$ClCH_2COOH + HOH \rightarrow \underset{\displaystyle OH}{\underset{|}{CH_2}}COOH + HCl$$

Chloroacetic acid

Glycolic acid

2. *Hydrolysis of cyanohydrins.* The hydrolysis of the cyanohydrins formed by the reaction of aldehydes and hydrocyanic acid gives an hydroxy acid containing one more carbon atom than the aldehyde; acetaldehyde under these conditions would yield α-hydroxypropionic or lactic acid.

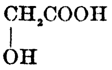


$$CH_3—\underset{\displaystyle OH}{\underset{|}{CH}}—CN + 2\,H_2O \xrightarrow{\text{Dilute acid}} CH_3—\underset{\displaystyle OH}{\underset{|}{CH}}—COOH + NH_3$$

Acetaldehyde cyanohydrin

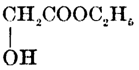
Lactic acid

Chemical Reactions of the Hydroxy Acids.—Since the hydroxy acids contain both the hydroxyl group characteristic of alcohols and the carboxyl group characteristic of acids, they would be expected to undergo the types of reaction characteristic of these two classes of compound. This is found to be the case. The carboxyl group forms salts, esters, and amides, and the hydrogen of the hydroxyl group can be replaced to form ethers.



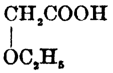
$$\begin{array}{l}CH_2COOH\\ |\\ OH\end{array}$$

Glycolic acid



$$\begin{array}{l}CH_2COOC_2H_5\\ |\\ OH\end{array}$$

Ethyl glycolate
(ester formation)

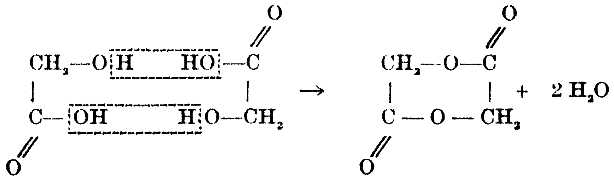


$$\begin{array}{l}CH_2COOH\\ |\\ OC_2H_5\end{array}$$

Ethyl glycolic acid
(ether formation)

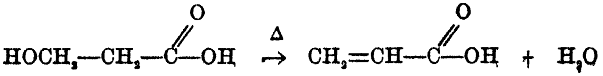
A unique situation exists in the case of the hydroxy acids, since the hydroxyl group characteristic of alcohols and the carboxyl group characteristic of acids are contained *in the same molecule.* Possibilities of new types of ester thus are presented.

1. α-Hydroxy acids, on warming or simply on standing over sulfuric acid, form cyclic compounds called *lactides.* These compounds can be considered as double esters or anhydrides since two molecules interact. The hydroxyl group of each combines with the carboxyl group of the other.



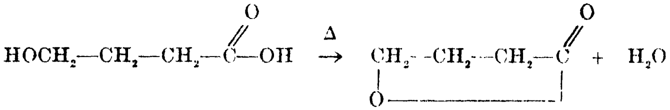
Glycolic acid Glycolic acid Glycolide
(a lactide)

2. On the other hand, β-hydroxy acids, on warming, easily split out water to give unsaturated acids. β-Hydroxypropionic acid yields water and acrylic acid.



β-Hydroxypropionic acid Acrylic acid

3. In the γ-hydroxy acids, the carboxyl group and the hydroxyl group are separated by a sufficient distance so that loss of water between them gives rise to stable cyclic compounds known as *lactones*. For example, γ-hydroxybutyric acid yields γ-butyrolactone.

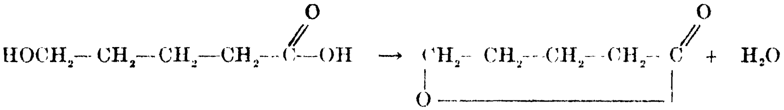


$$\mathrm{HOCH_2{-}CH_2{-}CH_2{-}\overset{O}{\overset{/\!/}{C}}{-}OH} \xrightarrow{\Delta} \underbrace{\mathrm{CH_2{-}CH_2{-}CH_2{-}\overset{O}{\overset{/\!/}{C}}}}_{\mathrm{O}} + \mathrm{H_2O}$$

γ-Hydroxybutyric acid γ-Butyrolactone

This type of cyclic structure is known as a *furane ring*.

δ-Hydroxy acids also yield lactones. δ-Hydroxyvaleric acid, on warming, is converted to δ-valerolactone. This cyclic structure, with five carbon atoms and one oxygen atom, is known as the *pyrane ring*. It is the type common to many sugars (see page 329).



$$\mathrm{HOCH_2{-}CH_2{-}CH_2{-}CH_2{-}\overset{O}{\overset{/\!/}{C}}{-}OH} \rightarrow \underbrace{\mathrm{CH_2{-}CH_2{-}CH_2{-}CH_2{-}\overset{O}{\overset{/\!/}{C}}}}_{\mathrm{O}} + \mathrm{H_2O}$$

δ-Hydroxyvaleric acid δ-Valerolactone

The lactones can be regarded as inner esters, since they are formed by the reaction of an hydroxy and a carboxyl group in the *same molecule*. Synthetic coconut flavor, γ-nonyl lactone, is being produced from castor bean oil.

Glycolic Acid, $CH_2OHCOOH$.—Glycolic acid, α-hydroxyacetic acid, occurs in unripe red grapes, sugar cane, grape foliage, and in the leaves of other plants. It can be prepared by boiling chloroacetic acid with water. Glycolic acid is a solid that is soluble in water, alcohol, and ether.

The sulfur analog of glycolic acid is named thioglycolic acid, $CH_2SHCOOH$. It is used in some depilatories.

Lactic Acid, $CH_3CHOHCOOH$.—Lactic acid is the α-hydroxy derivative of propionic acid. It can be prepared in the laboratory by the hydrolysis of the cyanohydrin of acetaldehyde. Lactic acid also can be prepared by the hydrolysis of the corresponding α-halogen acid. Most of the lactic acid used in commerce is produced by fermentation processes. Glucose, or corn sugar, obtained by the hydrolysis of corn starch, is heated to destroy any microorganisms that might be present, and then the sugar is inoculated with a pure culture of lactic acid bacteria. The fermentation is carried out at about 50° C. to retard the formation of butyric acid.

When the concentration of lactic acid increases beyond a certain point, the bacteria are inactivated; therefore, calcium or zinc carbonate is added to neutralize the acid as it is formed. The free acid is obtained from this sparingly soluble calcium salt by treatment with sulfuric acid.

Molasses also is used for this fermentation process.

Lactic acid is formed in the souring of milk by the action of lactic acid bacteria on lactose, the sugar in milk. Lactic acid first was isolated from sour milk by Scheele in 1780. The "curdling" that takes place during the natural souring of milk is a result of the formation of lactic acid. One of the proteins of milk, casein, is coagulated by the acid, and forms the curds.

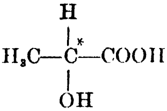
Lactic acid also is produced by the fermentation of lactose in whey, a by-product of the cheese industry or of the manufacture of casein.

Uses. Lactic acid is used in the leather industry for dehairing hides. It is used as an acidulant in fruit essences, syrups, and ice cream. Some formulas for infant feedings contain lactic acid as an ingredient. Calcium lactate is used in baking powders and in medicine to increase the calcium content of the blood. Silver lactate is employed as an antiseptic. Antimony and iron lactates are used as mordants in the dyeing of textiles. Lactic acid is a constituent of the transparent cast phenolic resins. Esters of lactic acid, such as ethyl lactate, are excellent solvents for nitrocellulose lacquers.

Aside from its industrial uses, lactic acid plays a prominent role in several natural fermentation processes. The conversion of cabbage to sauerkraut involves the action of lactic acid-forming bacteria. When the concentration of lactic acid becomes high enough, further fermentation is inhibited and the acid functions as a preservative. A similar condition exists during the formation of silage.

Lactic acid is one of the intermediate compounds formed in the process by which carbohydrates are converted into energy for muscle contraction (see page 615). This explains why lactic acid can be obtained from the press juice of lean meat. The acid isolated from this source is known as *sarcolactic* acid. This form of lactic acid differs in one important property from the lactic acid present in sour milk: that is, in its effect on polarized light. The difference between these two forms of lactic acid necessitates a discussion of a type of isomerism that we have not hitherto encountered.

Optical Isomerism.—An inspection of the graphic formula of lactic acid will reveal a feature that has been absent from most of the compounds considered thus far, and, for this reason, has not been pointed out.



$$\begin{array}{c} H \\ | \\ H_3C—\overset{*}{C}—COOH \\ | \\ OH \end{array}$$

Lactic acid

The carbon atom marked with an asterisk will be seen to have four *different* groups or atoms attached to it, and is designated as an asymmetric carbon atom. *An asymmetric carbon atom is defined as one whose valences are satisfied by four different kinds of atoms or groups.*

We can appreciate best the significance of an asymmetric carbon atom in a molecule if we return to the concept of the carbon atom situated at the center of a regular tetrahedron with the valences directed toward the corners. From purely geometrical considerations, if we represent the four different groups by A, B, C, and D, then there are two, and only two, possible spatial arrangements which cannot be superimposed. These two arrangements are represented by I and II in Fig. 34.

It is helpful for the student to manipulate models himself so that the three-dimensional space relationships involved will be appreciated. He is advised to construct models from corks or from atomic models made by pasting equilateral triangles of cardboard together to form regular tetrahedra.

The two arrangements, or forms (if actual compounds are being considered), bear the same relationship to each other as a right hand to a left hand. By the use of models, it will be seen that the two forms cannot be superimposed. Right and left hands can be placed together palm to palm, and they will coincide, but one cannot be superimposed on the other and made to coincide. A similar situation exists in the case of the two compounds. The two forms are said to be *mirror images* of each other, since the image in a mirror of either form has the struc-

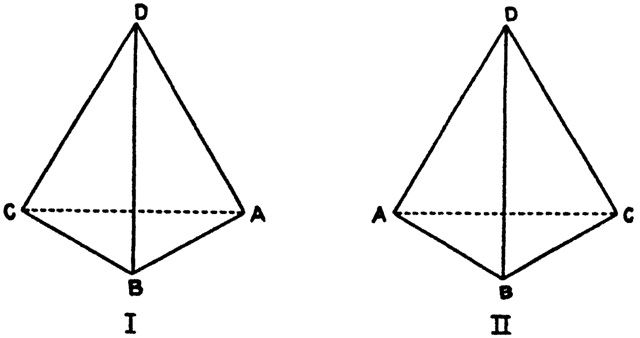


Fig. 34.—Spatial arrangement of groups in optical isomers. Models I and II are mirror images of each other and, if three-dimensional models are constructed, it is easily demonstrated that they cannot be superimposed.

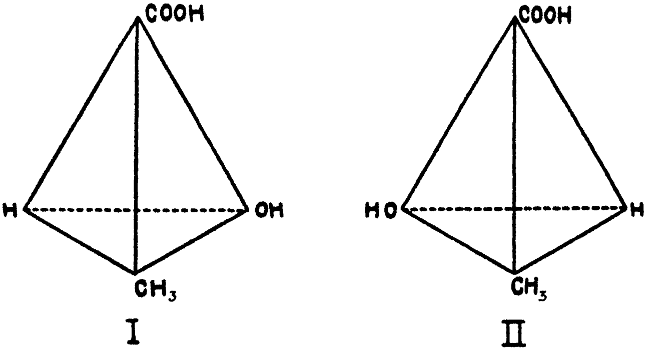
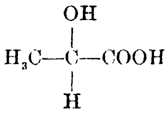


Fig. 35.—Optical isomers of lactic acid.

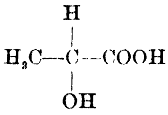
ture of the other one. The spatial relationship of the groups in the two forms of lactic acid are represented by I and II in Fig. 35.

The formulas for the optical isomers of lactic acid that are commonly encountered are really modifications of the projections of the three-dimensional figures on a flat surface. The conventional formulas of the two forms of lactic acid are:



$$H_3C-\overset{\displaystyle OH \atop |}{\underset{\displaystyle | \atop H}{C}}-COOH$$

(I)



$$H_3C-\overset{\displaystyle H \atop |}{\underset{\displaystyle | \atop OH}{C}}-COOH$$

(II)

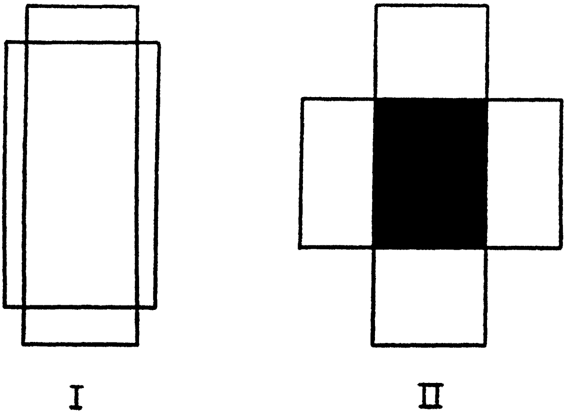


Fig. 36.—Polarizing action on light of Nicol prisms. In position I the prisms are parallel and light passes through both prisms. In position II the prisms are at right angles and light polarized by the first prism is screened out by the second.

One form of lactic acid is found to rotate plane polarized light to the right and is known as the dextro (sometimes abbreviated as D or +) form. The other form of lactic acid rotates the plane of polarized light exactly the same amount to the left and is known as the levo (sometimes abbreviated as L or −) form. Compounds such as these two forms of lactic acid, which differ from each other only in their effect on plane polarized light, are known as *optical isomers*, *optical antipodes*, or *enantiomorphic forms*. Substances that rotate the plane of polarized light are said to be optically active, or to possess optical activity.

It is necessary at this point to digress for a short explanation of what is meant by polarized light. Ordinary light is a form of energy propagated in the form of waves that are vibrating in all planes at right angles to the direction of propagation. If ordinary light is passed through a crystal of calcite, only two beams are transmitted. Each of these is vibrating in a plane perpendicular to the plane of vibration of the other. A Nicol prism is composed of two sections of calcite so cut and cemented together that one of the beams is refracted to the side; consequently, *the light that passes through it is vibrating only in one*

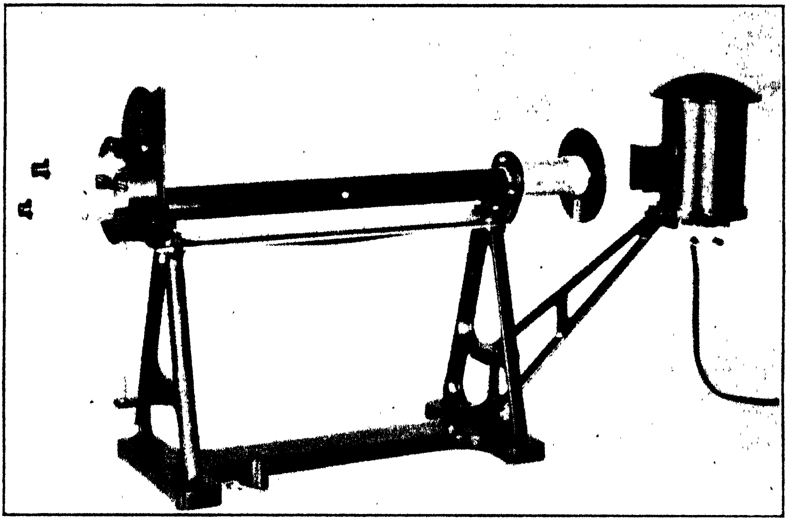


Fig. 37.—Polarimeter used for the accurate measurement of the rotation of polarized light by optically active substances. (Courtesy of the Bausch & Lomb Optical Co.)

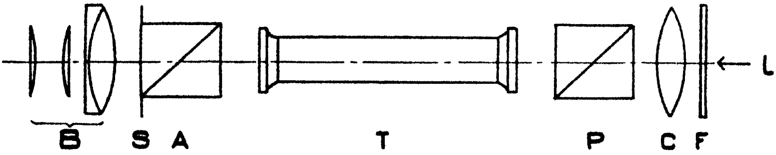


Fig. 38.—Diagram of the essential parts of a polarimeter. See text.

plane. Such light is said to be polarized, or since all of its vibrations are in one plane, it often is termed *plane polarized light.*

The polarizing action of a Nicol prism can be demonstrated easily by holding two such prisms between a source of light and the eye. When the axes of the prisms are in line, or parallel, the source of light is visible, but when the axes of the prisms are at right angles, the intersection of the two prisms is opaque. This is represented diagrammatically in Fig. 36.

The magnitude of rotation of plane polarized light by an optically active substance is measured in an instrument known as a polarimeter (Fig. 37). The essential parts of the polarimeter are shown in Fig. 38.

L is a source of light. Monochromatic light (light of one wave length) is required for polarimetric measurements, and can be obtained by passing light through a light filter made of a special kind of glass that transmits light of only one wave length. The source of light also can be an asbestos gauze saturated with sodium chloride and heated with a Bunsen burner. The sodium flame thus obtained gives practically monochromatic light.

F is a glass light filter, such as is used in the polarimeter illustrated in Fig. 37.

C is a condensing lens to concentrate the light on the polarizing prism.

P is a fixed Nicol prism for polarizing the light.

T is the sample tube in which the solution of optically active material is placed.

A is a movable Nicol prism known as the analyzer.

S is the scale that indicates the amount of rotation of the analyzer.

B represents a system of condensing lenses in the eyepiece for focusing on the field produced by the light passing through the analyzer. In addition, there is a similar set of lenses (not shown) in the upper telescope (Fig. 37) to magnify the small divisions on the scale, thus enabling an accurate reading of the degrees of rotation.

To increase the accuracy of the instrument, a small auxiliary Nicol prism often is placed at a slight angle to the polarizer.

In this case, the field of view in the eyepiece is divided into two halves. If the analyzer is set at an angle of 90 degrees to the plane of vibrations, that half of the field will be dark. When a solution of an optically active substance is placed in the sample tube, the dark half will become lighter and the division between the two halves will be indistinct. The analyzer is turned then until the original condition, obtained with only water in the sample tube, is restored. The amount of this rotation is read from the scale.

The amount of rotation of polarized light is dependent on several factors: (1) temperature, (2) wave length of light used, (3) concentration of the optically active substance in solution, and (4) length of the tube containing the solution. The formula for expressing the specific rotation of a compound is as follows:

$$[\alpha]_D = \frac{100\ a}{l\ c}$$

$[\alpha]$ = specific optical rotation.
D = the bright yellow line of the sodium spectrum.
a = observed rotation in angular degrees.
l = length of the tube in decimeters.
c = concentration in grams per 100 cc. of solution.

Values for specific rotation afford a means of comparing the optical activity of compounds. Particular compounds can be identified by their specific rotations, and as we shall see when we study the sugars, the amount of optically active substance present in a solution can be determined quantitatively by the magnitude of the optical rotation.

Sarcolactic acid from muscles is dextrorotatory. The levorotatory form is obtained when sugar is fermented by *Bacillus acidi levolactici.*

A mixture of equal amounts of the dextro and levo isomers has no effect on polarized light. The tendency of the levo form to rotate the light to the left is neutralized by the effect of the dextro form to rotate the light to the right. Such a mixture is known as a *racemic mixture.*

Lactic acid synthesized in the laboratory by the action of alkali on α-bromopropionic acid is a racemic mixture (optically inactive). This is the result of the operation of the law of probability. Billions of molecules are involved and the probability of forming the levo form is just as great as the probability of forming the dextro form.

By our definition of isomerism, dextrolactic and levolactic acids are isomers. They belong to the group of compounds having the type of isomerism termed stereoisomerism. The types of isomerism thus far encountered can be outlined as follows:

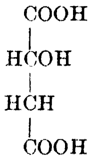
A. Chain or nuclear isomerism. Involves branching of the carbon chain, as in the isomeric pentanes.

B. Position isomerism. Due to the position of a particular group in the molecule, as in normal and isopropyl alcohol.

C. Stereoisomerism. Due to differences in spatial relationships.

  1. Geometric isomerism. Cis and trans isomers, which differ in physical and chemical properties, as in maleic and fumaric acids.
  2. Optical isomerism. Isomers named dextro and levo; same properties except effect on plane polarized light.

Malic Acid.—The most important monohydroxy derivative of a dicarboxylic acid is malic acid, which also can be termed monohydroxysuccinic acid.



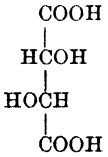
$$\begin{array}{c}\mathrm{COOH}\\ |\\ \mathrm{HCOH}\\ |\\ \mathrm{HCH}\\ |\\ \mathrm{COOH}\end{array}$$

Malic acid

Malic acid was discovered by Scheele in 1785 in unripe gooseberries. It is the chief acid of sour apples, from which source it derives its name (Latin *malum*, apple). It occurs also in cherries, rhubarb stalks, and the sap of the sugar maple. When this sap is evaporated during the manufacture of maple syrup, the calcium salt of malic acid separates out and forms the "sand" that collects in the vats. It is a by-product in the manufacture of apple syrup ("apple honey"), a hygroscopic agent added to cigarettes. Mountain ash berries also can serve as a source of malic acid.

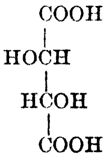
It will be noted from the formula that malic acid, like lactic acid, contains an asymmetric carbon atom, and is, therefore, optically active. It exists in three modifications: dextromalic acid, levomalic acid, and an optically inactive racemic mixture. The acid obtained from natural sources is the levo form. Its principal importance is its occurrence in the above-mentioned fruits.

Tartaric Acid.—Tartaric acid, dihydroxysuccinic acid, can exist in four distinct forms. This is possible because it contains two asymmetric carbon atoms, both of which have linked to them the same set of four different groups.



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{HOCH} \\ | \\ \mathrm{COOH} \end{array}$$

Dextrotartaric acid (active)

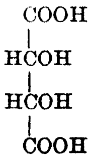


$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HOCH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{COOH} \end{array}$$

Levotartaric acid (active)

Equal molecular mixture of the dextro and levo forms

Racemic mixture (inactive)



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{HCOH} \\ | \\ \mathrm{COOH} \end{array}$$

Mesotartaric acid (inactive)

The classical investigations of Pasteur on the separation of the salts of tartaric acid were instrumental in leading to the theory of stereoisomerism. In 1848, when Pasteur was searching for an explanation of the optical inactivity of racemic acid, he observed that crystals of sodium ammonium tartrate that had formed below 27° C. were of two kinds. These crystals bore the relation to each other of object to image, or as the right hand to the left hand. His keen curiosity is indicative of his greatness as a scientist, for he laboriously separated the two kinds of crystal with the aid of tweezers and a hand lens. To his delight, he found that when one of the piles of crystals was dissolved in water, polarized light was rotated to the right, while a solution of the other kind of crystals rotated polarized light an equal amount to the left. He thus discovered levotartaric acid, the dextro form having been known before that time. Thus, the reason for the optical inactivity of the racemic acid was explained.

Pasteur found that by heating cinchonine D-tartaric acid, a derivative of tartaric acid, an inactive form of the acid, from which an active form could not be obtained, was produced. The reason for the inactivity of this form, termed mesotartaric acid, was not explained in Pasteur's time. During the next quarter of a century, the speculations and hypotheses of scientists resulted in the tetrahedral concept of the asymmetric carbon atom. This theory was proposed in 1874 by both van't Hoff and LeBel, working independently. The tetrahedral concept of the carbon atom already has been discussed in connection with the optical activity of lactic acid (see page 248).

Since the two asymmetric carbon atoms in tartaric acid have the same groups attached to them, they will affect plane polarized light in the same way, and thus there are three possible arrangements for the asymmetric carbon atoms.

+ A	- A	+ A
+ A	- A	- A
dextro	levo	meso

In these examples, A represents an asymmetric carbon atom and the signs represent the direction of rotation of polarized light by this particular carbon atom. Hence, in the first case, the effect on plane polarized light of one asymmetric carbon atom will be enforced by the other. A similar situation exists in the second case, the difference being that the asymmetric carbon atoms are mirror images of the first case; hence, the rotation is in the opposite direction. In the third case, one asymmetric carbon atom rotates polarized light to the right, and the other rotates it to the left. Since these effects are exactly equal, there is no observable effect on polarized light. This is the situation existing in mesotartaric acid. Mesotartaric acid is said to be inactive due to *internal compensation.*

Methods of Resolution.—The separation of a racemic mixture into its optically active components is known as *resolution.* The methods of resolving a racemic mixture are important, especially in the preparation of pharmaceutical compounds, since in a number of instances life processes can utilize only one of the two optically active isomers. For example, D-lactic acid is completely utilized by higher animals, while L-lactic acid is almost completely excreted. There are three principal methods of resolution.

1. *Mechanical.* This was the method first used by Pasteur. It is applicable only to the cases in which large, well-defined crystals of the dextro and levo types are formed. Such crystals result when sodium ammonium tartrate is crystallized below 27° C.

In some cases, however, the dextro and levo isomers form a molecular *compound,* which consequently gives only one form of crystal. In such a case, obviously it is impossible to separate the two forms by hand-picking. Such combinations are known as *racemates* or *racemic compounds.* At relatively high temperatures dextrotartaric and levotartaric acids form a racemate, the melting point of which is 206° C.

2. *Biological.* The second method of obtaining optically active forms from an optically inactive racemic mixture depends on the fact that certain fungi and molds growing in a racemic mixture feed preferentially on one of the two optically active forms, leaving the other unchanged. It is thus possible to obtain the unconsumed form in the optically pure state. For example, when the mold, *Penicillium glaucum,* is grown in a solution of the racemic mixture of a salt of tartaric acid, it consumes the dextro form and leaves the levo form. A disadvantage of this method is that it allows for the separation of only one form, and this is very often the one that does not occur naturally.

3. *Chemical.* The method used most frequently for the separation of optically active isomers from a racemic mixture is the chemical one. If an optically active base, such as L-cinchonine, is added to a solution of racemic tartaric acid, two kinds of salts are formed: D-tartaric-L-cinchonine and L-tartaric-L-cinchonine. These salts are not mirror images of each other, because L-cinchonine is present in each; hence they have different properties, such as solubility. The L-tartaric-L-cinchonine salt is the least soluble, and, on evaporation of a solution, crystallizes out first. When the two salts have been separated by repeated crystallizations, the L-cinchonine can be hydrolyzed off by the action of dilute acid or alkali; and pure D-tartaric acid can be

obtained from one fraction, and pure L-tartaric acid from the other. This process of resolution also was introduced by Pasteur.

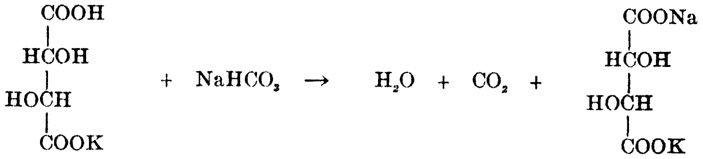
Racemization.—The process of racemization is the opposite of resolution. In most instances this change from the optically active to the optically inactive form is undesirable from the standpoint of utilization of the compound by living cells. Thus it is important to know how to avoid a loss of optical activity. Racemization occurs most rapidly in the presence of hydroxyl ions. Often, heating with water for long periods of time will result in the formation of a racemic mixture.

Dextrotartaric Acid.—The four forms of tartaric acid have been discussed at some length because of their importance in illustrating the theory of optical activity. The only form that is used commercially is dextrotartaric acid. It is distributed widely in nature, being present in sumac berries, cucumbers, and pineapple. It constitutes 40 per cent of the total acids of Concord grapes.

The principal commercial source of dextrotartaric acid is the wine industry, of which it is a by-product. When grape juice ferments in the manufacture of wine, the acid potassium salt of tartaric acid settles out as a result of its low solubility in dilute alcohol. The crude deposit in the wine cask is known as *lees.* These lees are recrystallized once to give a product called *argol,* or crude tartar. A precipitate of argol often separates from unfermented grape juice that has been concentrated. The pure potassium acid tartrate obtained by the further purification of argol is known as *cream of tartar.*

Dextrotartaric acid can be prepared from the crude argol or from cream of tartar by first treating it with milk of lime to form the calcium salt. Then the free acid is liberated from the calcium salt by treatment with sulfuric acid, and is purified by recrystallization. Tartaric acid is a solid, readily soluble in water and alcohol, with a melting point of 170° C.

Potassium acid tartrate is mixed with sodium bicarbonate (baking soda) in the cream of tartar type of baking powder. These active ingredients are diluted with starch, which also aids in keeping the mixture dry. When water is added, the acid group of the tartrate becomes active and liberates carbon dioxide from the baking soda. The carbon dioxide acts as the leavening agent.

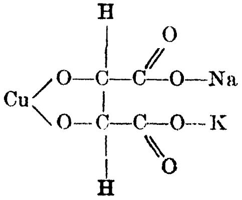


$$\begin{array}{c}\text{COOH}\\ |\\ \text{HCOH}\\ |\\ \text{HOCH}\\ |\\ \text{COOK}\end{array} + \text{NaHCO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2 + \begin{array}{c}\text{COONa}\\ |\\ \text{HCOH}\\ |\\ \text{HOCH}\\ |\\ \text{COOK}\end{array}$$

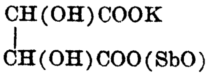
Potassium acid tartrate Sodium bicarbonate Rochelle salt

Sodium potassium tartrate, or Rochelle salt, is used as a purgative in Seidlitz powders, in which it is mixed with sodium bicarbonate and free tartaric acid.

Rochelle salt also is a component of Fehling's solution. Its function is to form a soluble copper compound that prevents precipitation of copper hydroxide, and yet furnishes a sufficient quantity of copper ions for the reaction. The complex salt formed is deep blue in color, and probably has the following formula:



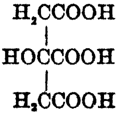
Potassium Antimonyltartrate, Tartar Emetic.—



$$\begin{array}{l}\text{CH(OH)COOK}\\ |\\ \text{CH(OH)COO(SbO)}\end{array}$$

Tartar emetic is used in medicine in the treatment of parasitic diseases. It is employed also as a mordant in dyeing.

Citric Acid.—



$$\begin{array}{c}\text{H}_2\text{CCOOH}\\ |\\ \text{HOCCOOH}\\ |\\ \text{H}_2\text{CCOOH}\end{array}$$

Citric acid is a monohydroxytricarboxylic acid. It is not related in structure to any of the common simple acids. It is one of the most widely distributed organic acids in the plant kingdom. It is found in highest concentration in citrus fruits, but it is present also in many other fruits, such as currants, raspberries, cranberries, and strawberries. Citric acid accounts for over 80 per cent of the organic acids in pineapple.

The acid is prepared chiefly in Italy and California from inferior lemons, which contain from 5 to 6 per cent of it. The citric acid in the press juice is precipitated as the insoluble calcium salt, and the free acid subsequently is obtained by treatment of the salt with sulfuric acid. In Hawaii the acid is prepared from waste in the pineapple canneries.

A large part of the citric acid used for industrial purposes is produced by the fermentation of sugars by certain molds, such as *Citromycetes*. About 26,000,000 pounds of this acid are produced annually by the citrus and fermentation industries.

Citric acid is a solid, very soluble in water and alcohol. It is used for the preparation of synthetic lemonade, and is the organic acid most widely used in the manufacture of soft drinks. It finds use as a mordant in cotton textile printing.

Salts of citric acid. Magnesium citrate, mixed with sodium bicarbonate and sugar (''citrate of magnesium''), is sold as a mild laxative.

Sodium citrate is used to prevent the coagulation of blood. Often when blood is obtained for the quantitative determination of calcium and phosphorus, as in balance studies on dairy cattle, it is desirable to secure a sample of whole blood. The added citric acid salt prevents the formation of a clot. Small amounts of sodium citrate (3 to 5 g. per liter) are being used to prevent the clotting of blood in ''blood banks.''

Ferric ammonium citrate is one of the compounds used in making blueprint paper.

Ketonic Acids

Pyruvic Acid, $CH_3COCOOH$.—Pyruvic acid is the simplest ketonic acid. It also can be designated as α-ketopropionic acid.

It is prepared by the distillation of tartaric acid with potassium bisulfate. It is a liquid with a pungent odor and a boiling point of 165° C. Pyruvic acid contains both a ketone and a carboxyl group, and therefore gives the reactions typical of these groups. The carboxyl group forms salts and esters, while the ketone group reacts with carbonyl reagents, for example, with hydroxylamine, to give the oxime.

Pyruvic acid is of interest because it is one of the intermediate products of the oxidation of glucose in the body (see page 614).

Acetoacetic Acid, CH_3COCH_2COOH.—Acetoacetic acid is a representative of the β-ketonic acids. It is one of the "ketone bodies" present in the urine of persons suffering from diabetes mellitus. The acetoacetic acid easily decomposes to form acetone. This is the source of the acetone sometimes present in the breath and in the urine of diabetic patients.

$$\underset{\text{Acetoacetic acid}}{CH_3COCH_2COOH} \rightarrow \underset{\text{Acetone}}{CH_3COCH_3} + CO_2$$

Acetoacetic ester, more properly called ethyl acetoacetate, is a more important compound than the acid itself. This ester, the Grignard reagents, and the malonic ester are the three most frequently used reagents in synthetic organic chemistry. Acetoacetic ester is prepared by the action of metallic sodium on ethyl acetate in the presence of 2 to 3 per cent of ethyl alcohol.

$$\underset{\text{Ethyl acetate}}{CH_3COOC_2H_5 + CH_3COOC_2H_5} \xrightarrow[C_2H_5OH]{Na} \underset{\substack{\text{Acetoacetic}\\ \text{ester}}}{CH_3COCH_2COOC_2H_5} + \underset{\text{Ethyl alcohol}}{C_2H_5OH}$$

The reaction takes place in several steps. From the standpoint of the end products, the reaction can be considered as an aldol condensation between two molecules of ethyl acetate. For a discussion of the mechanism of the reaction the student should consult an advanced textbook of organic chemistry.*

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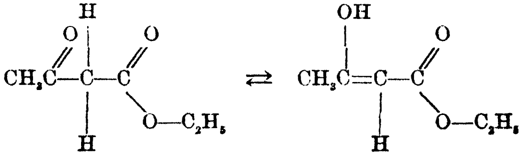
*Karrer, P.: Organic Chemistry, New York, 1938, Nordemann Publishing Co., Inc., page 240.

Acetoacetic ester has some peculiar properties that puzzled scientists for years, and were the subject of many investigations. The usual reactions of a ketone group, such as reactions with hydrocyanic acid, hydroxylamine, and sodium bisulfite, are given by acetoacetic ester, as would be expected. In addition, it gives reactions characteristic of an hydroxy group. These reactions include (1) the formation of a compound with metallic sodium similar to the compounds formed from alcohols and sodium; and (2) the production of a deep red color with ferric chloride, a result given also by hydroxy compounds known as phenols, which we shall discuss later.

No one formula could be assigned that would explain satisfactorily these two types of reaction, and the explanation was proposed that acetoacetic ester existed simultaneously in two forms. Later researches proved this to be true. One of the hydrogens of the active methylene group can shift to the carbonyl group, giving a hydroxyl group, and at the same time forming a double bond.

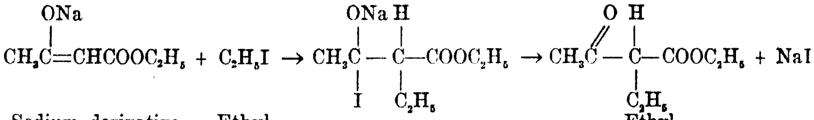


Keto form Enol form

Careful experimental work has demonstrated that, at room temperatures, acetoacetic ester consists of an equilibrium mixture containing about 8 per cent of the hydroxy (enol) form and 92 per cent of the keto form. If a reagent is added that reacts with one form, more of this form will be generated by intramolecular rearrangement, which maintains the equilibrium condition.

Acetoacetic ester illustrates what is sometimes termed *dynamic isomerism*. More often, however, this type of isomerism, in which a compound passes back and forth from one structural form to another, is known as *tautomerism*.

Reactions of acetoacetic ester. Acetoacetic ester is used for the synthesis of substituted acids and ketones. The sodium derivative of the enol form is used for the syntheses. It results from the action of sodium on the ester. This sodium derivative reacts with alkyl halides to yield compounds in which the alkyl group is attached *directly* to carbon, and not, as might be expected, to oxygen.



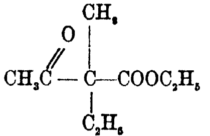
$$CH_3\overset{ONa}{\overset{|}{C}}{=}CHCOOC_2H_5 + C_2H_5I \rightarrow CH_3\underset{I}{\overset{ONa}{C}}-\underset{C_2H_5}{\overset{H}{C}}-COOC_2H_5 \rightarrow CH_3\overset{O}{\overset{\|}{C}}-\underset{C_2H_5}{\overset{H}{C}}-COOC_2H_5 + NaI$$

Sodium derivative of acetoacetic ester

Ethyl iodide

Ethyl acetoacetic ester

The second hydrogen on the methylene group can be replaced with an alkyl group by a similar series of reactions to give ethyl methyl acetoacetic ester.

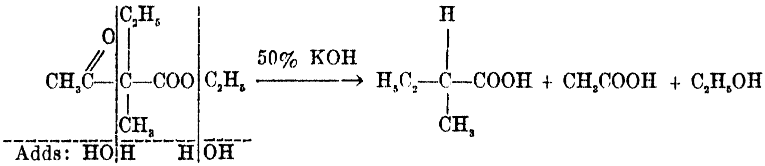


$$CH_3\overset{O}{\overset{\|}{C}}-\underset{C_2H_5}{\overset{CH_3}{C}}-COOC_2H_5$$

Ethyl methyl acetoacetic ester

Two types of compounds can be obtained from these alkylated acetoacetic esters, depending upon the conditions of hydrolysis.

1. When the alkyl-substituted acetoacetic ester is hydrolyzed with 40 to 50 per cent potassium hydroxide, substituted acetic acids are formed; hence this type of hydrolysis is known as *acid hydrolysis.*



$$CH_3\overset{O}{\overset{\|}{C}}-\underset{CH_3}{\overset{C_2H_5}{C}}-COO\;C_2H_5 \xrightarrow{50\%\ KOH} H_5C_2-\underset{CH_3}{\overset{H}{C}}-COOH + CH_3COOH + C_2H_5OH$$

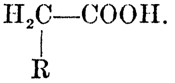
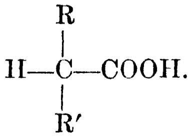
Ethyl methyl acetoacetic ester (reacting with water)

Methyl ethyl acetic acid

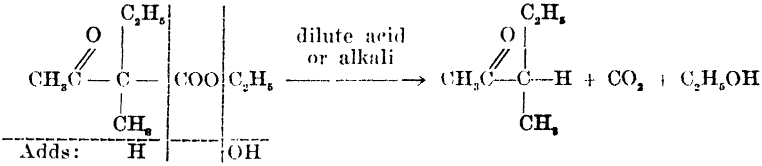
Acetic acid

Ethyl alcohol

The dotted lines are to indicate where the molecule splits and where the elements of water add during the hydrolysis.

If only one hydrogen of the methylene group of acetoacetic ester is substituted by an alkyl group, hydrolysis by concentrated alkali yields a monosubstituted acetic acid having the type formula  $\underset{R}{\underset{|}{H_2C}}—COOH$. When both hydrogens are substituted, a disubstituted acetic acid is formed on hydrolysis. These acids have the type formula  $H—\overset{R}{\overset{|}{\underset{R'}{\underset{|}{C}}}}—COOH$. The methyl ethyl acetic acid produced in the above reaction is an example of a disubstituted acetic acid.

2. Hydrolysis with dilute acids or alkalies yields an alkyl-substituted ketone. Because of the type of compound obtained, this type of hydrolysis usually is referred to as *ketone hydrolysis.*

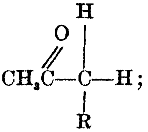


Ethyl methyl acetoacetic ester (reacting with water)

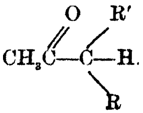
Methyl isobutyl ketone

Ethyl alcohol

By means of the ketonic hydrolysis, it is possible to synthesize monosubstituted ketones of the type formula:



or disubstituted ketones:



From these reactions it can be seen that acetoacetic ester is an exceedingly valuable compound for a wide variety of chemical syntheses.

Industrially it is used for the preparation of antipyrine, a compound that reduces fever, and for acetoanilide, a dye intermediate.

Study Questions

1. How might the substituted acids be defined?
2. What is the explanation for the fact that trichloroacetic acid is a much stronger acid than acetic acid? Write the formula for trichloroacetic acid. Name a use of this compound.
3. Using different substituting atoms and groups, demonstrate the operation of the system that uses Greek letters to locate the position of the substituted group.
4. What are *lactims?* Show an equation for the formation of a lactim from lactic acid. How do lactims differ from *lactones?* What property of the hydroxy-substituted acids makes possible the formation of these two structures?
5. Distinguish between a *furane ring* and a *pyrane ring.*
6. Why can the lactones be regarded as inner esters?
7. How do you explain chemically the formation of curds in sour milk?
8. What are some industrial uses of lactic acid and its salts?
9. Of what biological significance is lactic acid?
10. Define an *asymmetric carbon atom.* What physical property does it bestow upon compounds that possess such an arrangement?
11. What is polarized light? How can it be obtained?
12. What are *antipodes* or *enantiomorphic forms?*
13. How do you explain the fact that lactic acid as synthesized in the laboratory is a racemic mixture?
14. Dextrolactic and levolactic acids illustrate what type of isomerism? Give examples of the types of isomerism encountered thus far.
15. Write the graphic formula for malic acid, indicating the asymmetric carbon atom with an asterisk.
16. Write structural formulas for the four possible forms in which tartaric acid can exist.
17. How did Pasteur discover L-tartaric acid?
18. How do you explain the fact that mesotartaric acid is optically inactive despite the fact that it contains two asymmetric carbon atoms?
19. Describe the three possible methods of resolving a racemic mixture.
20. What is meant by *racemization?*
21. From what is tartaric acid made commercially? What is an important use of the potassium salt of tartaric acid?

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CHAPTER XII

LIPIDS

Definition.—The class of compounds known as lipids constitutes a part of the tissues of plants and animals, and takes part in the normal chemical reactions of living things. Just as the term trees includes many subdivisions, so the term lipid also is capable of a number of subdivisions. In general, however, lipids can be defined as *substances insoluble in water; soluble in the fat solvents, such as ether, chloroform, and carbon tetrachloride; and related to fatty acids as esters, actual or potential.* That is to say, lipids actually are fatty acid esters, or they are compounds capable of taking part in the formation of esters. The classification of the lipids will help to clarify this point.

Classification.—The classification of the lipids proposed by Dr. W. R. Bloor is as follows:

1. Simple lipids—esters of the fatty acids with various alcohols
    - a. Fats and oils—glyceryl esters of fatty acids
    - b. Waxes—esters of fatty acids with high molecular weight monoatomic alcohols
2. Compound lipids—esters of fatty acids that contain groups in addition to alcohol and fatty acids
    - a. Phospholipids—substituted fats containing phosphoric acid and a nitrogenous base: lecithins, cephalins, sphingomyelins
    - b. Galactolipids—compounds of the fatty acids with a carbohydrate; they also contain nitrogen, but no phosphoric acid: kerasin, phrenosin, nervon, and oxynervon
3. Derived lipids—substances that are derived from the simple and compound lipids by hydrolysis, and that are soluble in the fat solvents
    - a. Sterols—high molecular weight cyclic alcohols
    - b. Free fatty acids

Simple Lipids

Fats and Oils.—The fats and oils are the simplest class of lipid. They are all esters formed from the triatomic alcohol, glycerol, and fatty acids. Fats and oils are the same type of chemical compound; however, at ordinary room temperature (20° C.) those that are solids generally are referred to as fats, whereas those that are liquids are called oils.*

Fats and oils occur abundantly in nature. Edible nuts contain high percentages of fat; for example, almonds contain 55 per cent; Brazil nuts, 66 per cent; and walnuts, 64 per cent fat. Some fruits also have a high content of fat; avocados and olives are both approximately 20 per cent fat. Cereals, such as wheat, corn, and rye, have fat deposited in the seed embryo. Many plant seeds, such as cottonseed, poppyseed, and soybean, contain high percentages of oil and serve as commercial sources of oils.

Fats are an excellent source of food from an energy standpoint. They supply 9 Calories per gram, approximately twice as many Calories per gram as proteins or carbohydrates supply. In the animal body, fats serve as a reserve food. Body fat is stored as a layer under the skin, and around the organs in the abdominal cavity. Some is interspersed in muscular tissue. In addition to serving as a reserve food supply, fat in the animal body acts in some instances as a protective padding. Organs covered with fat are thus protected against blows and bruises. Since fat is a poor conductor of heat, it serves as insulation against cold (loss of body heat).

Everyone is familiar with such edible fats as butter, lard, fat meat, hydrogenated shortenings, and cooking oils. In addition to serving as an important class of foodstuffs, fats and oils play a part in many industrial processes, such as the manufacture of ointments and creams, paint and varnish industries, soap manufacture, candlemaking, food preservation, and as a source of glycerol. Neatsfoot oil is obtained from the skin, bones, and feet of cattle (exclusive of hoofs). The first quality oil is used for lubricating watches and fine machinery. The second grade oil is used in the textile and leather industries.

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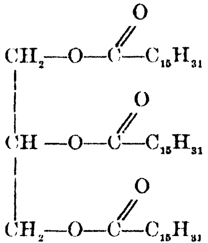
*These oils are not to be confused with mineral and lubricating oils, which are pure hydrocarbons and not esters. Essential oils also are not fats.

All fats and oils are either simple or mixed glyceryl esters of fatty acids. Tripalmitin can be taken as an example of a typical fat. Its structural formula is shown below:

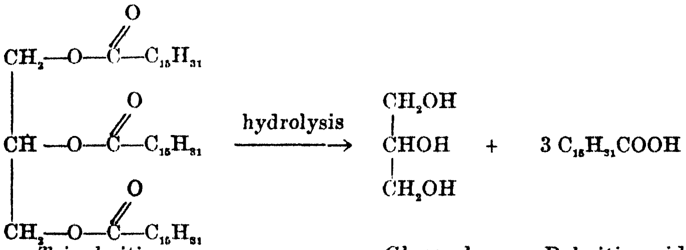


Tripalmitin

Tripalmitin is an example of a simple glyceride, since all the fatty acids linked to the glycerol molecule are the same (palmitic acid). It is probable that most fats in nature are mixed, rather than simple, glycerides. That is to say, the glycerol molecule is usually esterified with two, or even three, different kinds of fatty acid.

Since all the fats are derivatives of glycerol, their names can be prefaced with the word glyceryl. Thus, the foregoing simple fat can be called glyceryl tripalmitate. However, in common usage the glyceryl part of the name is dropped, and the *ate* suffix is changed to *in*, as in tripalmitin; or even more simply, palmitin.

Hydrolysis of Fats.—The hydrolysis of fats to free fatty acids and glycerol can be accomplished by superheated steam alone, or more easily by the use of acid, certain enzymes, or alkali.



Tripalmitin Glycerol Palmitic acid

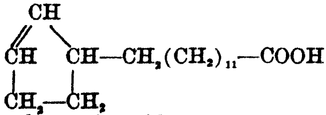
Hydrolysis catalyzed by strong acids is employed in the manufacture of the free fatty acids. The diet of most animals consists partially of fats, which are hydrolyzed by an enzyme *lipase,* present in the digestive tract. The hydrolysis of fats, using an alkali, is called *saponification,* and is the reaction used in the manufacture of soap. (See page 276.)

Fatty Acid Constituents.—With the exception of isovaleric acid, only the normal fatty acids containing an even number of carbon atoms are constituents of natural fats. The reason for this fact has not been established. Table XII shows the system used for classifying the fatty acids and cites some typical sources of the different esters.

Of the saturated acids, palmitic and stearic occur most abundantly. These two acids occur in practically all animal and vegetable fats. They are obtained by the hydrolysis of such fats as tallow, lard, coconut oil, and palm oil, are sold under the name stearin, and are used for candlemaking. Some wax or paraffin is added to a mixture of the acids to prevent crystallization before the mass is molded into candles. The free acids, rather than the glyceryl esters, are used in making candles, for the esters would decompose to yield glycerol, which upon being heated would break down to the vile-smelling aldehyde, acrolein ($CH_2{=}CH{-}CHO$).

Of the unsaturated fatty acids containing one double bond, oleic acid occurs most abundantly. Along with palmitic and stearic acids, it is present in almost all animal and vegetable fats. In liquid vegetable oils it accounts for 20 per cent or more of the total fatty acid constituents.

Chaulmoogric and hydrocarpic acids are cyclic fatty acids that occur in chaulmoogra oil.



Chaulmoogric acid

The oil has been found effective in the treatment of leprosy. This dreaded disease, caused by *Mycobacterium leprae,* has attracted attention from the earliest times in history. Frequent

TABLE XII

CLASSIFICATION OF FATTY ACIDS

SERIES	FATTY ACID	TOTAL NUMBER OF C ATOMS IN MOLECULE	OCCURRENCE
Saturated ($C_nH_{2n+1}COOH$) Fatty Acids	Butyric	4	Butter fat
	Isovaleric	5	Dolphin and porpoise oil
	Caproic	6	Coconut and palm kernel oil, butter fat
	Caprylic	8	Coconut and palm kernel oil, butter fat
	Capric	10	Coconut and palm kernel oil, butter fat
	*Lauric	12	Coconut oil, babassu kernel oil
	*Myristic	14	Nutmeg oil (74 per cent), myrtle wax, coconut and palm kernel oil
	*Palmitic	16	Palm oil, animal and vegetable fats
	*Stearic	18	Cacao butter, most solid plant and animal fats
	Arachidic	20	Peanut oil
	Lignoceric (isomers)	24	Pisang wax, carnauba wax
	Cerotic	26	Beeswax, carnauba wax
	Melissic	30	Many waxes
Unsaturated Fatty Acids			
Oleic acid series ($C_nH_{2n-1}COOH$) (one double bond)	Tiglic	5	Croton oil
	*Oleic	18	Very widely found, olive oil a rich source
Linoleic acid series ($C_nH_{2n-3}COOH$) (two double bonds)	*Linoleic	18	Vegetable oils, such as linseed and cottonseed
Linolenic acid series ($C_nH_{2n-5}COOH$) (three double bonds)	*Linolenic	18	Linseed oil, soybean oil, sunflower oil, tung oil
	Elaeostearic	18	Chinese wood oil, tung oil
Unsaturated Hydroxy Acids			
	Ricinoleic ($C_{17}H_{32}(OH)—COOH$)	18	Forms over 80 per cent of the total acids in castor oil
Cyclic Acids			
	Hydnocarpic	16	Chaulmoogra oil
	Chaulmoogric	18	Chaulmoogra oil

*The starred acids are those most widely distributed in nature.

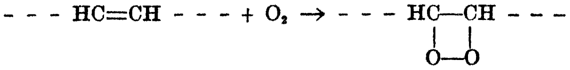
references to it are made in the Bible. Even today it is not uncommon throughout Asia, parts of Africa, the Hawaiian and Philippine Islands, and in scattered sections of the United States.

The use of chaulmoogra oil for the treatment of leprosy developed from observations that natives in the Far East who were afflicted with the disease obtained relief by rubbing their wounds with the oil. About 1918, Dr. Rogers, a British surgeon in India, converted chaulmoogra oil to the corresponding soap by treatment with sodium hydroxide. He found that in aqueous solution this soap gave more satisfactory results when injected than hitherto had been obtained by any other treatment.

About the same time, Dr. Dean, then head of the chemistry department at the University of Hawaii, found that a very effective substance for treating leprosy could be made by heating chaulmoogra oil with alcohol and a little sulfuric acid. This ester proved to be a better substance for the treatment of the disease than the oil, and it has been administered intramuscularly with some success.

Rancidity.—Rancidity in fats is of two different kinds, oxidative and hydrolytic. Hydrolytic rancidity is the result of the hydrolysis of the glycerides with the liberation of free fatty acids. This type of rancidity is caused by the presence of lipases or microorganisms. Since the fatty acids of high molecular weight are tasteless, this kind of rancidity is noticeable only in fats containing the low molecular weight fatty acids, such as butter and coconut oil. In butter, 10 to 13.6 per cent of the fatty acids are of the volatile (short chain) type.

The other type of rancidity is due to oxidation of the fats by atmospheric oxygen. The saturated fatty acids are not oxidized by contact with the air, but the unsaturated fatty acids are the ones attacked. The first step probably is the formation of peroxides at the double bonds.



$$- - - \mathrm{HC{=}CH} - - - + \mathrm{O_2} \rightarrow - - - \begin{array}{c}\mathrm{HC{-}CH}\\ |\quad\;|\\ \mathrm{O{-}O}\end{array} - - -$$

Double bond in fatty acid Fatty acid peroxide

These compounds subsequently decompose or react with one another to form aldehydes, ketones, fatty acids, active oxygen, ozone, and hydrogen peroxide. However, the typically disagreeable odor of rancid fats is due primarily to the medium molecular weight aldehydes formed. Actually only about 0.1 per cent of the fat decomposes to form these compounds. Heat, light, moisture, and practically all metals except aluminum and nickel tend to hasten oxidative rancidity.

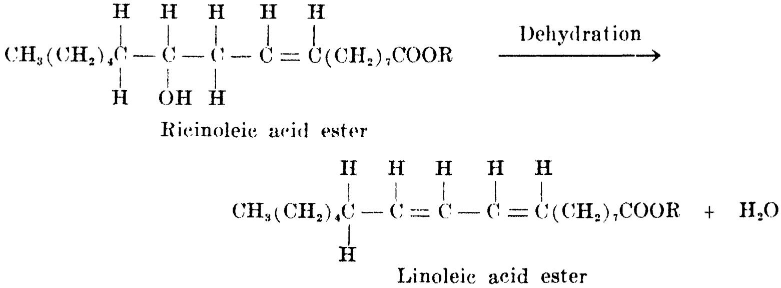
Rancidity can be retarded by such precautionary measures as keeping the fat cool, storing fat in colored containers and thus keeping it away from the light, and by excluding air.

Antioxidants.—All fats and oils contain natural antioxidants. Their function is to protect the fat or oil from deterioration during its normal life. Vegetable oils contain a larger proportion of natural antioxidants than do animal fats. The amazing thing about antioxidants is their unusual effectiveness in extremely low concentrations. As little as a few hundredths, or even thousandths, of 1 per cent suffice to protect the products from rancidity for considerable lengths of time. The tocopherols (see vitamin E, page 731) are effective natural antioxidants.

A great many compounds have been successfully used commercially as antioxidants. Among those found effective are hydroquinone, pyrogallol, quinhydrone, pyrocatechol, and gallic acid. The addition of 0.05 per cent of gum guaiac to lard markedly reduces its tendency to become rancid, thus eliminating one of the objections to this type of shortening. At this concentration the antioxidant has no noticeable effect on the flavor or odor.

Drying Oils.—Closely related to the process of rancidity is the reaction such oils as linseed, tung, and oiticia undergo when they are exposed to the air. A thin layer of the oil will take up oxygen and form a tough, elastic, waterproof surface. Such oils are called drying oils, and are characterized by containing a high percentage of unsaturated fatty acid glycerides. For example, linseed oil contains approximately 48 per cent linoleic acid, and 34 per cent linolenic acid, in the combined form. Tung oil, originally obtained exclusively from China, now is being obtained in ever-increasing amounts from tung trees growing in Texas, Florida, Georgia, Alabama, and Mississippi. It contains approximately 85 per cent of elaeostearic acid ester.

Large quantities of castor oil are now commercially dehydrated, and the resulting oil compares favorably with tung oil in drying properties. The oil contains over 80 per cent of ricinoleic acid, which upon dehydration is converted to linoleic acid, thus accounting for the drying properties of the resulting oil. This process came into importance during World War II because of the acute shortage of linseed and tung oil.



$$CH_3(CH_2)_4\underset{H}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-\overset{H}{C}=\overset{H}{C}(CH_2)_7COOR \xrightarrow{\text{Dehydration}}$$

Ricinoleic acid ester

$$CH_3(CH_2)_4\underset{H}{\overset{H}{C}}-\overset{H}{C}=\overset{H}{C}-\overset{H}{C}=\overset{H}{C}(CH_2)_7COOR + H_2O$$

Linoleic acid ester

Drying oils form the basis for the manufacture of paints. Essentially, oil paints are pigments suspended in a drying oil. When the paint is spread in a thin layer and exposed to the air, the pigment is firmly held in place by the tough film formed. Certain products known as "driers" are added to oil paints to accelerate the drying process. Turpentine, and lead, manganese, and cobalt salts of unsaturated fatty acids are used for this purpose. Driers do not increase the amount of oxygen eventually taken up by the oil, but merely hasten the process.

The first step in the drying of the oils is the oxidation to peroxides. As more oxygen is absorbed and higher molecular weight, complex oxygen-containing compounds are formed, the process proceeds at a slower rate. It has been shown that a thin film of linseed oil will absorb 16 per cent of its weight of oxygen.

The linoleum industry also uses drying oils, chiefly linseed. Linoleum is a mixture of powdered cork, pigments, and drying oil, which is spread in a thick layer on a cloth back and allowed to harden.

Linseed oil, the chief drying oil of commerce, is obtained from the seed of the flax plant. A different variety of flax plant is cultivated for seed purposes than is grown for linen. In the United States, the chief states growing seed flax are North and South Dakota, Minnesota, and Montana. The oil content of the seed varies from 35 to 40 per cent. The oil is obtained from the seeds by first heating to 85° C. in order to soften the seed tissues. This treatment then is followed by expression of the oil in hydraulic presses giving pressures as high as 4,000 pounds per square inch. The oil is purified and refined by chemical means, and this product is known as raw linseed oil.

In quick-drying processes boiled linseed oil is used. This is produced by heating the oil to a temperature as high as 125° C. Air is blown through the oil, and driers are added. The advantage of the boiled oil over the raw product is that a part of the oxidation already has taken place, and the time necessary for drying is thus shortened.

Hydrogenation.—In recent years a large industry has developed for transforming liquid oils into solid fats. The student will recall that the only difference between oils and solid fats is in the number of double bonds in the fatty acids; in other words, in the amount of hydrogen the compound contains. If an oil is heated under pressure to about 200° C. in the presence of a catalyst, such as finely divided nickel, hydrogen will add at the double bonds. If the process is continued long enough, completely saturated fatty acids will result. Such hydrogenated shortenings as "Crisco," "Spry," and "Snowdrift" are made from vegetable oils.

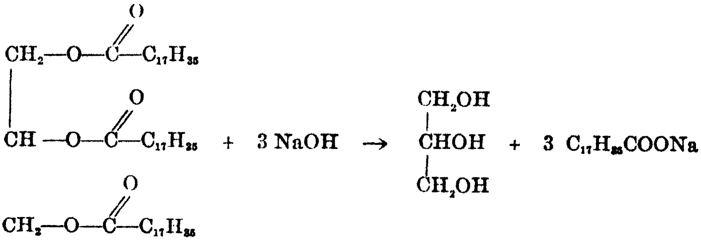
Hydrogenation is not carried to completeness, for if it were, the resulting fat would be a hard, brittle product resembling tallow. Instead, the hydrogenation is carried only to the point where a fat of desired workability and firmness is obtained. Crisco contains 20 to 25 per cent saturated fatty acids, 65 to 75 per cent oleins, and 5 to 10 per cent linoleins.

Hydrogenated shortenings owe part of their popularity to the fact that they do not easily become rancid on standing, as do butter and lard. A hydrogenated shortening can be left in the kitchen cupboard for weeks in the summer while the family is away on vacation and still retain its original freshness.

A shortcoming of hydrogenated fats is that they do not have the shortening power of other fats, such as lard. Shortening power is rather a poorly defined property, but the function of a shortening agent is to act as a lubricant for the tough fibers of protein in a baked product. This property of acting as a lubricant for tough, fibrous material is somewhat analogous to the process that takes place if peanuts are taken into the mouth when one is chewing gum. It soon will be found that the resiliency of the gum has been lost and that the gum is disintegrating. Along this same line, it can be mentioned that the most successful way of removing chewing gum from fabrics is to rub the gum with a fat until it disintegrates; the fat then can be removed with carbon tetrachloride or some other fat solvent.

It has been shown that, if a fatty acid contains a double bond, it has nearly double the shortening power of a corresponding saturated fatty acid. This property is explained by the "bending" of the fatty acid at the point of the double bond. Fats whose fatty acids contain two or three double bonds thus can be expected to have greatly increased shortening power over that of a saturated fat.

Soap Manufacture.—Fats react with alkalies to form soaps, the reaction being termed *saponification*. Thus, *soaps* are salts of fatty acids. The ordinary toilet and laundry soaps of commerce are chiefly mixtures of the sodium salts of stearic, palmitic, and oleic acids. The formation of a typical soap can be illustrated by the reaction of sodium hydroxide with tristearin.



Tristearin

Glycerol

Sodium stearate (a soap)

Soap is prepared commercially by boiling animal or vegetable fats with sodium hydroxide. The sodium soap formed is insoluble in brine solution, so salt is added to the reaction mixture. The soap rises to the top of the brine solution and can be removed. The glycerol and excess lye remain in the residual brine. The glycerol can be removed from the residual liquid by vacuum distillation. The molten soap can be dried in large frames, or on heated rollers, or can be spray dried. The last process yields the now popular quickly dissolving laundry soap granules or beads, such as "Super Suds."

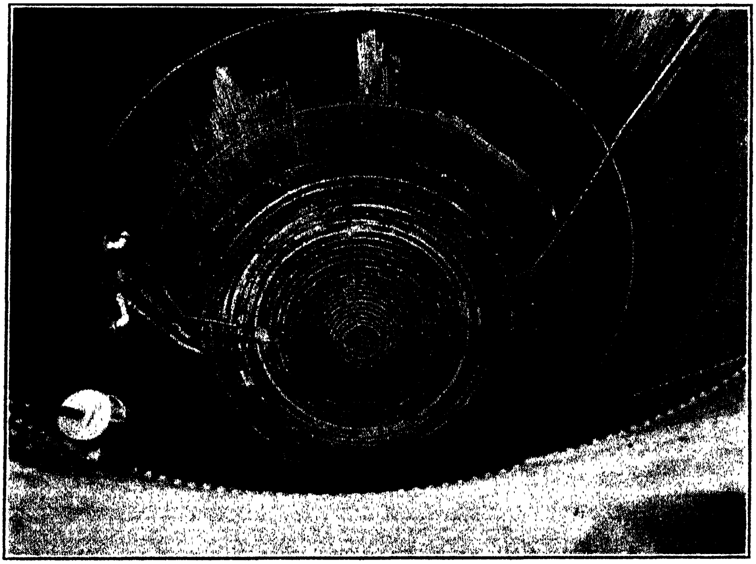


Fig. 39.—Saponification on a large scale. An empty soap kettle that is three stories deep. Such a kettle is stocked for each batch with approximately 130,000 pounds of fat and 75,000 pounds of caustic solution, from which a yield of about 150,000 pounds of toilet soap and 14,000 pounds of glycerin are obtained. (Courtesy of Procter and Gamble Co.)

The character of the soap formed is dependent largely on the fatty acids present in the fat. If a high percentage of sodium palmitate and sodium stearate are formed, the soap will be firm in texture. If, however, the soaps of unsaturated fatty acids are formed, such as sodium oleate, the soap will be soft, and perhaps liquid, at ordinary temperatures. This explains why many oils are unsatisfactory for soap making. If, however, the oils are first hydrogenated, satisfactory soaps can be made from them. Soaps made from fatty acids with less than 12 carbon atoms have low detergent properties but sud freely, while those made from fatty acids containing more than 18 carbon atoms do not dissolve readily in water at ordinary temperatures. Thus in the soap industry there is quite a science to the selection, preparation, and blending of fats and oil used in saponification to yield products with the desired degree of sudsing ability, detergent efficiency, and cake firmness.

Soaps that float are made by blowing air into the soap before it is formed into cakes, and the ability to float is not dependent upon the purity of the soap. Transparent soaps are made by dissolving the soap in alcohol and evaporating off the solvent. Scouring soaps contain such abrasives as silica, pumice, or lava dust. Frequently such substances as sodium carbonate or trisodium phosphate are added to scouring soaps to serve as water softeners in ''hard water.''

At this point in the discussion, it is necessary to explain what is meant by hard water, and why such water impairs the efficiency of the ordinary sodium soaps. Hardness in water is of two kinds, temporary and permanent. Temporary hardness is due to the presence of calcium bicarbonate, $Ca(HCO_3)_2$, and magnesium bicarbonate, $Mg(HCO_3)_2$. Such hardness is called temporary because it can be removed by boiling. Permanent hardness is due to the presence of calcium sulfate, $CaSO_4$, and magnesium sulfate, $MgSO_4$, in the water.

The *sodium* and the *potassium* soaps are the only common *soluble* soaps. The other metallic soaps are insoluble in water. Thus, when a sodium soap is added to water containing calcium and magnesium ions, those metallic ions replace the sodium in the soap and the insoluble calcium and magnesium soaps are precipitated. These insoluble soaps cling to clothes in laundering and are very difficult to rinse out.

The ''softening'' of water simply means the removal of the calcium and magnesium ions from the water.* Soap itself is a water softener in the sense that it reacts with hard water to precipitate the insoluble calcium and magnesium soaps, but this method of softening water is very wasteful of soap. The soap exerts no cleansing action until it first has reacted to remove all the calcium and magnesium ions from the water. It is desirable, therefore, to use a cheaper means to remove the calcium and magnesium ions before soap is added.

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*Raymore (Soap Sanit. Chemicals 22: 48, 1946) on the basis of a study of the ability of various soaps to yield permanent lathers in water of varying hardness found that, if $1.65 worth of soap per year per family were required with water of zero hardness, then the cost of soap with waters of 10 and 35 grains of hardness would be $8.99 and $28.42, respectively. Hardness of 10 grains per gallon is common.

Boiling is one way of softening water, because insoluble calcium and magnesium carbonate are formed from the corresponding bicarbonates, and precipitate out. Only temporary hardness can be removed in this way. The scale that collects on the inside of teakettles is largely calcium and magnesium carbonate removed from hard water by boiling. However, boiling is not a practical means of softening large quantities of water. Chemical methods of precipitating the calcium and magnesium ions offer a much quicker, cheaper, and more convenient way to soften hard water.

All chemical water softeners are effective because they precipitate calcium and magnesium ions from the water in some insoluble form. To illustrate the reaction of the different chemical water softeners, calcium sulfate and calcium bicarbonate will be considered as the substances causing the hardness. Magnesium bicarbonate and magnesium sulfate would react in the same manner.

Trisodium phosphate (Na_3PO_4) is an effective and inexpensive water softener. The amount of this chemical required to soften a given quantity of water can be calculated if the "grains of hardness" in the water supply are known. This information can be supplied by the local water company.

$$\underset{\substack{\text{Calcium}\\ \text{sulfate}}}{3\,CaSO_4} + \underset{\substack{\text{Trisodium}\\ \text{phosphate}}}{2\,Na_3PO_4} \rightarrow \underset{\substack{\text{Calcium}\\ \text{phosphate}}}{Ca_3(PO_4)_2\downarrow} + \underset{\substack{\text{Sodium}\\ \text{sulfate}}}{3\,Na_2SO_4}$$

Since trisodium phosphate dissolves slowly, it is desirable to use a saturated solution of the compound for softening water in order to obtain the full effectiveness of the product.

Sodium carbonate (Na_2CO_3) (washing soda) also acts as a water softener, since both calcium and magnesium carbonates are insoluble compounds.

$$\underset{\substack{\text{Calcium}\\ \text{sulfate}}}{CaSO_4} + \underset{\substack{\text{Washing}\\ \text{soda}}}{Na_2CO_3} \rightarrow \underset{\substack{\text{Calcium}\\ \text{carbonate}}}{CaCO_3\downarrow} + \underset{\substack{\text{Sodium}\\ \text{sulfate}}}{Na_2SO_4}$$

Borax ($Na_2B_4O_7.10H_2O$) is a softener commonly used in households. It is not a good softener for the permanent types of hardness, but it is effective in removing temporary hardness. It hydrolyzes to give sodium hydroxide, which acts as the softening agent.

$$Ca(HCO_3)_2 + 2\,NaOH \rightarrow CaCO_3\downarrow + Na_2CO_3 + 2\,H_2O$$

In the eastern part of the United States are found "natural green sands" capable of softening water. These sands are sodium silicoaluminate compounds, and are called zeolite softeners. They react with hard water by withdrawing the calcium and the magnesium ions and replacing them with sodium.

$$\underset{\text{Zeolite}}{Na_2O.2Al_2O_3.5SiO_2} + \underset{\substack{\text{Calcium}\\ \text{sulfate}}}{CaSO_4} \rightarrow CaO.2Al_2O_3.5SiO_2\downarrow + \underset{\substack{\text{Sodium}\\ \text{sulfate}}}{Na_2SO_4}$$

When this type of softener is used, arrangement is made so that the water to be softened flows through a tank filled with zeolite. After continued use the softening power of the zeolite is exhausted. The zeolite can be regenerated simply and easily by pouring strong brine solutions through the container. The sodium in the brine replaces the calcium and magnesium, and thus the zeolite is ready to be used over again.

Synthetic ion exchange resins, which are condensation products of phenol sulfonic acids and formaldehyde, have been developed for the softening and dealkalizing of water. In many cases these synthetic materials have a faster ion exchange rate and a greater capacity than the natural green-sand zeolites.

All soaps have antiseptic properties, but these are increased by addition of phenolic substances, such as carbolic acid diphenyl sulfide, and diphenyl methane.

The cleansing properties of soluble soaps can be attributed to the fact that they are emulsifying agents. They lower surface tension and cause particles of dirt or grease to become suspended in water.

Soaps other than the sodium ones are manufactured commercially. Soft or liquid soaps usually are potassium salts of the unsaturated fatty acids. The *tincture of green soap* used in hospitals is a solution of potassium soap in alcohol. Zinc stearate is a component of most talcum powders. Lead, manganese, and cobalt soaps are used in paints as driers. Some calcium soaps, which are soluble in oil, are components of lubricating greases. Ferric stearate is used as a leather dressing.

Sodium ricinoleate is a soap that deserves special mention. All bacteria that are harmful produce chemical substances called toxins. These toxins are poisonous and cause the symptoms of disease. Sodium ricinoleate changes many bacterial toxins to harmless substances. It is sometimes used in treating those types of "food poisoning" due to the ingestion of food contaminated with toxins.

Fat Analysis.—Certain chemical constants are useful in characterizing the various fats. One of these is the saponification number. Roughly speaking, it varies inversely with the molecular weight of the fat; that is, the higher the molecular weight the lower the saponification number. For example:

	Molecular weight	Saponification number
Tributyrin	302.2	557.0
Tripalmitin	806.8	208.6
Tristearin	890.9	188.9

The saponification number is defined as the number of milligrams of potassium hydroxide required to saponify one gram of fat. If the fat has a high molecular weight, there will be fewer carboxyl groups per unit of weight; hence, less potassium hydroxide will be needed for the saponification reaction than will be required if the fat contains low molecular weight acids. To illustrate this fact, the gram of fat used as a standard in determining saponification number can be likened to a bushel basket. If the basket is filled with baseballs which represent high molecular weight fatty acids with one carboxyl group each, a certain number of balls will be required. If the basket is filled with marbles representing low molecular weight fatty acids also with one carboxyl group each, a much larger number will be needed.

Iodine Number.—Iodine in a reactive form (ICl or IBr) will combine directly with the unsaturated fatty acids in fats at the double bonds. Thus, the amount of iodine that will combine with a fat is a measure of the degree of unsaturation and is characteristic of the particular fat. *The iodine number of a fat can be defined as the number of grams of iodine absorbed by 100 grams of fat.*

If a weighed sample of fat is treated with reactive iodine and found to take up a given number of grams of iodine, the iodine number of the fat can be calculated by setting up a simple proportion. For example, let us suppose that 5 grams of fat were found to react with 4 grams of iodine. To obtain the iodine number, we must determine the grams of iodine that would react with 100 grams of fat. The following proportion expresses the desired relationship:

$$\begin{aligned} 5 : 100 &:: 4 : X \\ 5X &= 400 \\ X &= 80 \end{aligned}$$

Thus, the iodine number of the fat is 80.

A frequently used way of grouping fats and oils is according to their iodine numbers. Table XIII illustrates this classification.

TABLE XIII

IODINE NUMBERS OF COMMON FATS AND OILS

CLASS	NAME	IODINE NUMBER
Nondrying oils (iodine numbers below 100)	Butter	26- 28
	Cocoa butter	32- 41
	Coconut butter	6- 10
	Olive oil	79- 88
	Peanut oil	88- 98
Semidrying oils (iodine numbers below 130)	Cottonseed oil	103-111
	Maize or corn oil	111-128
	Soybean oil	122-134
Drying oils (iodine numbers above 130)	Linseed oil	175-202
	Tung oil	163-171
	Dehydrated castor oil	145-190

The iodine number is used to determine the extent of hydrogenation in commercial processes of hydrogenating oils.

Reichert-Meissl Number.—The volatile fatty acids, which can be steam distilled, are comprised chiefly of the C_4 to the C_{12} acids. The Reichert-Meissl number is a measure of the amount of these volatile fatty acids in a fat. It is defined as the number of cubic centimeters of 0.1 N alkali required to neutralize the volatile fatty acids from 5 grams of fat. Butter has a particularly high Reichert-Meissl number because of its relatively high content of such low-molecular weight acids as butyric and caproic.

Waxes.—Waxes, another group of simple lipids, are esters of fatty acids with high-molecular weight alcohols. The term should not be used loosely to include all compounds with a waxy consistency, since this would include paraffin wax. Paraffin is a hydrocarbon, and does not yield an alcohol and acid on hydrolysis, as do the true waxes.

The common alcohols and fatty acids found in waxes are:

Alcohols		Acids	
Cetyl	$C_{16}H_{33}OH$	Lignoceric	$C_{23}H_{47}COOH$
Carnaubyl	$C_{24}H_{49}OH$	Cerotic	$C_{25}H_{51}COOH$
Ceryl	$C_{26}H_{53}OH$	Melissic	$C_{29}H_{59}COOH$
Myricyl	$C_{31}H_{63}OH$	Palmitic	$C_{15}H_{31}COOH$

Beeswax is approximately 80 per cent myricyl palmitate, 10 to 12 per cent free cerotic acid, and 10 to 18 per cent free hydrocarbons.

Carnauba wax is obtained from the leaves of the carnauba palm grown in Brazil. The wax forms a heavy layer on both the upper and the lower sides of the leaf to prevent evaporation of water. The climate where the carnauba palm grows is very hot and dry most of the year. Usually there is about one rainfall a year, and that in the form of a flood; thus, it is imperative that the leaves conserve moisture. One locality in Brazil is the only place in the world where the climatic conditions are such that the deposits of carnauba wax are of sufficient thickness to be of commercial importance. Five adult palm trees are capable of producing about one pound of wax annually. About 10,000 tons of the wax were produced in Brazil in 1935, the United States importing approximately half of this supply. Carnauba wax is used in polishes for floors, automobiles, furniture, and shoes. It is used in candles to raise the melting point, in phonograph records, in soap, and in carbon paper.

Spermaceti wax is obtained from the sperm whale. In the head of this whale there is a large cavity that can hold nearly a ton of an oily liquid. When this is cooled below the body temperature of the whale, a waxy solid crystallizes out. This is spermaceti wax, and the oil left is known as sperm oil. The principal ester present in spermaceti is thought to be cetyl palmitate. Spermaceti is used in candlemaking, in cosmetics, and in pharmacy. Sperm oil is a high-grade lubricant used for special purposes, such as oiling watches and delicate instru-

Fig. 40.—The first step in the harvesting of carnauba wax in the arid regions of northeastern Brazil. Laborers are harvesting the wax-coated leaves by means of a sharp, sickle-like knife fastened to the end of a long pole. The leaves are dried and the wax is beaten off with clubs by native workers. The powdered wax then is melted down and allowed to solidify into cakes. In this form the wax is shipped mainly to the United States, to be manufactured into polishes for floors, automobiles, furniture, and shoes. (Courtesy of S. C. Johnson and Sons, Inc.)

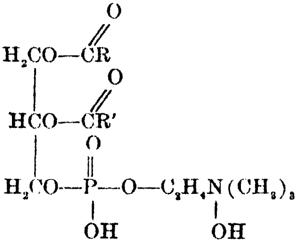
ments, where it is essential to use a lubricant that will not form a gummy deposit.

Wool wax, or lanolin, a by-product of the scouring of wool for textiles, is a basis for many ointments and creams. It forms an emulsion with water, and is used as a base for ointments that carry a water-soluble material as an active ingredient. Lanolin can be used alone or in combination with other materials for finishing, softening, and preserving leather. It is an ingredient of varnishes and quick-drying paints.

Compound Lipids

Phospholipids.—Phospholipids are components of all animal and vegetable cells. In addition to the elements contained in the simple lipids, compound lipids contain nitrogen and phosphorus. The phospholipids have been divided into three distinct classes: lecithins, cephalins, and sphingomyelins.

Lecithins. Lecithins are glycerides containing residues of two molecules of fatty acids, phosphoric acid, and a nitrogen-containing base, choline. A typical lecithin has the following structural formula:



A typical lecithin

Lecithins are good emulsifying agents and form stable emulsions in water. It appears likely that fats are partly converted to lecithins in the body, and are transported in this form from one tissue to another by the blood. Lecithins are important sources of the phosphoric acid used in building new cells in the body.

In the laboratory, crude lecithin can be obtained from egg yolk by extracting with ether and precipitating out the lecithins with acetone. Commercially, it is obtained from soybeans.

Lecithins are used in candy making to prevent a "bloom" (white spots) from developing on chocolates and to reduce the viscosity of chocolate coating mixtures without the addition of the relatively expensive cocoa butter. They are used in the petroleum industry chiefly to inhibit gum formation in lubricants.

Cobra venom contains an enzyme called lecithinase A. This enzyme catalyzes the loss of one fatty acid molecule from lecithin molecules. The substance that remains after the loss of the fatty acid is called a lysolecithin. Lysolecithins cause hemolysis (disintegration of red blood cells), thus accounting in part for the toxicity of cobra venom. The chief effect of the poison is on the nervous system.

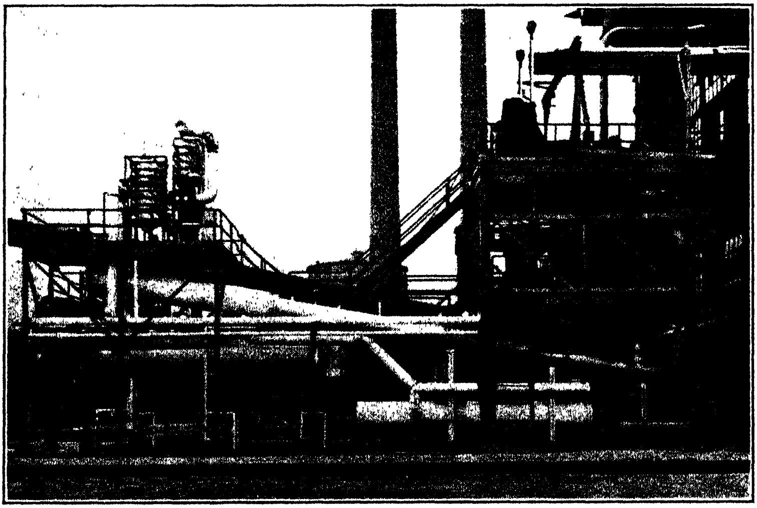
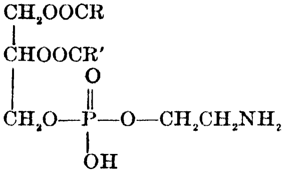


Fig. 41.—Solvent extraction plant for soybeans. One of the principal solvents is n-hexane, which extracts lecithins as well as the oil. Lecithins are used in the candy industry, in gasolines to prevent corrosion, and in the formation of oil-in-water emulsions. Soybean oil is a component of many paints and varnishes. The protein obtained from the "cake" after the oil has been removed is being used in the manufacture of plastics, and recently, a synthetic fiber has been made from this protein material. (Courtesy of the Ford Motor Co.)

Cephalins. Cephalins, or kephalins, differ from lecithins only in the kind of base they contain. Instead of choline, most cephalins contain colamine, or β-aminoethyl alcohol. Cephalins have the following structural formula:

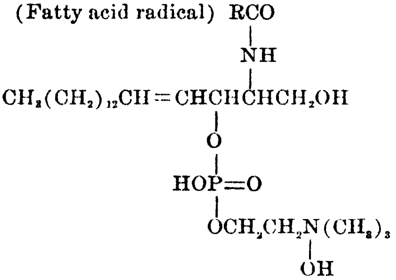


A typical cephalin

It has been found that some cephalins contain serine ($CH_2OH.$-$CHNH_2COOH$) or inositol (see page 719) instead of colamine. Commercial "soya lecithin" is derived from soybeans, and contains about one-third lecithin and two-thirds cephalin.

Cephalins are important in blood clotting. It is believed that the disintegration of blood platelets to release cephalin is the first step in blood coagulation. In certain diseases, known as purpuras, where the blood platelets are greatly reduced in number, the patient may bleed to death.

Sphingomyelins. The third type of phospholipid, sphingomyelin, is not a glyceryl ester as are lecithins and cephalins. On hydrolysis sphingomyelins yield fatty acids, phosphoric acid, choline, and sphingosine. Its probable formula is as follows:



A sphingomyelin

Sphingomyelins are found in brain and nerve tissues. They have not been isolated from plant tissues. Large quantities of phospholipids, chiefly sphingomyelins, accumulate in the liver and spleen of children suffering from Niemann-Pick's disease. This disease is rapidly fatal, and occurs chiefly in the first two years of life. Fortunately, Niemann-Pick's disease is rare.

Galactolipids.—The galactolipids, known also as glycolipids or cerebrosides, occur chiefly in the brain and nerve tissues. On hydrolysis, they yield fatty acids, sphingosine, and the sugar galactose. They differ from one another in the kind of fatty acids they contain. The galactolipids that have been well characterized are kerasin, phrenosin, nervon, and oxynervon.

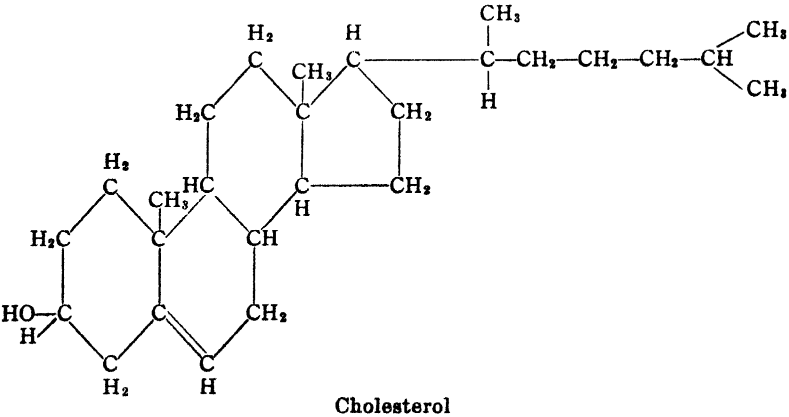
Derived Lipids

By definition, the derived lipids are substances that are obtained from the simple and compound lipids by hydrolysis, and that are soluble in the fat solvents but insoluble in water. This last qualification excludes glycerol, choline, colamine, phosphoric acid, and galactose—all compounds derived from compound lipids, but soluble in water rather than in fat solvents.

The two important types of derived lipid remaining are the free fatty acids, which have been discussed already (see page 270), and the *sterols*, which are high-molecular weight cyclic alcohols.

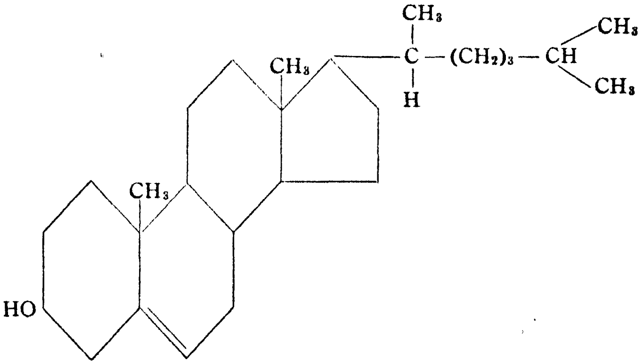
The best known sterol is cholesterol, found only in animal tissues and originally isolated from gallstones. The name cholesterol is derived from Greek words, *chole* meaning bile, and *stereos* meaning solid. Cholesterol is found in every living cell in the body; it exists in the blood stream partly as free sterol, and partly in chemical combination with fatty acids. It is found in largest amount in the tissues of the nervous system and comprises about 14 per cent of the white matter of the brain.

The chemical structure that has been established for cholesterol is as follows:



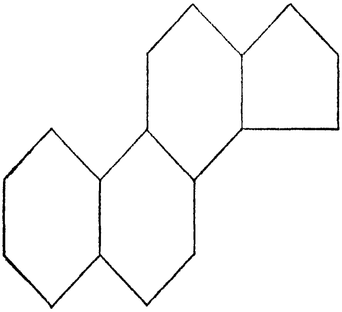
Cholesterol

In order to simplify the writing of such complicated structures as that for cholesterol, a shorthand method of representing carbon rings is used. The hydrogens attached to each carbon atom in the ring are omitted for the sake of convenience.



Cholesterol

Cholesterol and the other sterols have a cyclopentanoperhydrophenanthrene nucleus, which has been designated by the shorter term, cholane. It can be diagrammed as:



Cholane nucleus

Sterols are found also in plants. A number have been isolated, and collectively they are known as phytosterols. Ergosterol is a sterol found in certain lower plants (the fungi). It is a potential source of vitamin D, which is formed when the sterol is exposed to ultraviolet radiant energy.

The sex hormones (Chapter XXVIII) contain the same kind of nucleus as the sterols, and so are related structurally to the sterols.

Study Questions

1. Define lipids and make an outline of their general classification.
2. Give the names of three fats obtained from plant sources.
3. What are four uses of fats?
4. What alcohol do all fats yield on hydrolysis? Write the structural formula for tristearin.
5. What is the name of the fatty acid series containing one double bond, two double bonds, and three double bonds? Name specific fatty acids belonging to each series.
6. What fatty acids have been shown to be essential in the diet of rats?
7. Leprosy sometimes is treated by the use of what oil?
8. What are four ways of hydrolyzing fats? What are the end products of hydrolysis?
9. What are the two types of rancidity and what causes each kind? Give measures that might be taken to retard these kinds of rancidity.
10. What are peroxides? Write a probable equation for the formation of one.
11. What are some typical drying oils? How do drying oils differ from cooking oils?
12. In simple terms describe what takes place during hydrogenation. What advantages and disadvantages do hydrogenated shortenings have over cooking oils?
13. What term is applied to the reaction of a fat and an alkali? Write the equation for the reaction of tripalmitin and sodium hydroxide, naming the products of the equation.
14. Why could not a satisfactory toilet soap be made by the reaction of cottonseed oil and sodium hydroxide?
15. What is the cause of *temporary hardness* and *permanent hardness* in water? How does soap act to soften hard water?
16. Write an equation to illustrate how boiling acts to soften water.
17. Upon what principle do all chemical water softeners work? Write equations to show how several different types of chemical water softeners act to soften permanent hard water.
18. What is zeolite? Of what practical importance is the compound?
19. How can saponification number be defined? Would butter or lard have the higher saponification number?
20. How can iodine number be defined? What property of fats does it measure?
21. What is Reichert-Meissl number?

22. Name four waxes and tell for what they are used. Why is paraffin not a true wax?
23. What is the formula for a typical lecithin? What are some uses of lecithin?
24. How do cephalins differ in structure from lecithins? What is the possible function of cephalins in the body?
25. What compounds are obtained from sphingomyelins on hydrolysis?
26. What products are yielded by the galactolipids on hydrolysis?
27. Why is cholesterol classed with the derived lipids? Diagram the nucleus that is common to cholesterol, ergosterol, and the sex hormones.
28. The molecular weight of linolenic acid is 278. Calculate its iodine number.
29. The hydrolytic type of rancidity in butter results in the formation of what undesirable compound?
30. Describe briefly the manufacture of boiled linseed oil.
31. What is the phospholipid that functions in the permeability of the cell membrane?
32. What is the name of the sterol that can be converted into vitamin D by irradiation with ultraviolet light?
33. Explain why linseed oil is widely used in paints.

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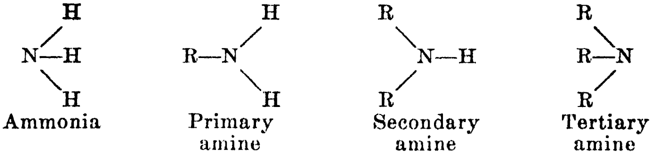
CHAPTER XIII

AMINES AND MISCELLANEOUS NITROGEN COMPOUNDS

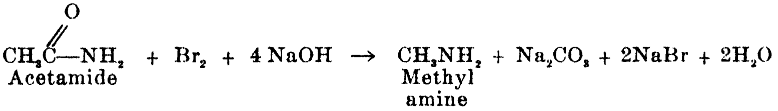
Amines

Introduction.—From the standpoints of structure and of properties, amines can be considered as alkyl derivatives of ammonia. Amines are grouped in three classes: primary, secondary, and tertiary, according to the number of alkyl (R) groups in the molecule.



Preparation of Primary Amines.—Methods of preparing methyl amine and ethyl amine will serve to illustrate the general methods for the preparation of primary amines.

1. Primary amines can be prepared from acid amides by the action of bromine or chlorine* and an alkali. This method first was used by A. W. Hofmann, and is known as the *Hofmann rearrangement.* It is a method frequently used for the preparation of primary amines.



$$\underset{\text{Acetamide}}{CH_3\overset{O}{\overset{/\!/}{C}}—NH_2} + Br_2 + 4\,NaOH \rightarrow \underset{\text{Methyl amine}}{CH_3NH_2} + Na_2CO_3 + 2NaBr + 2H_2O$$

The reaction takes place in three steps. These will be given in order that the student can understand better the mechanism of the reaction, and thus avoid blind memorization.

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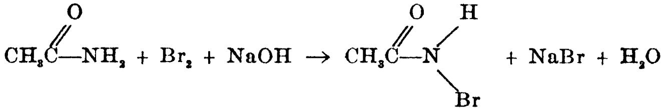
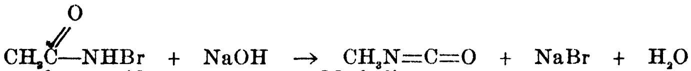
*The preparation of methylamine hydrochloride from acetamide by means of calcium hypochloride is described by C. R. Hauser and W. B. Renfrow, Jr. in J. Chem. Ed. 14: 542, 1937.

The first step consists in the replacement of one of the hydrogens of the amino (—NH_2) group by bromine, with the formation of a bromamide.



Acetamide Acetobromamide

In the second step, the bromamide, on heating with alkali, loses hydrogen bromide and rearranges to form the isocyanate.



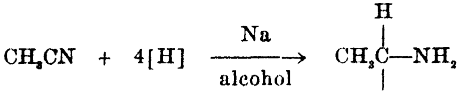
Acetobromamide Methylisocyanate

Thirdly, the isocyanate is hydrolyzed by the alkali to yield the amine and carbon dioxide. The latter reacts with sodium hydroxide to form sodium carbonate.

$$\underset{\text{Methylisocyanate}}{CH_3N{=}C{=}O} + 2\,NaOH \rightarrow \underset{\text{Methyl amine}}{CH_3NH_2} + Na_2CO_3$$

This synthesis yields primary amines containing one less carbon atom than the amide used as a starting material.

2. Primary amines can be prepared by the reduction of the corresponding nitrile or cyanide.



$$CH_3CN + 4[H] \xrightarrow[\text{alcohol}]{\text{Na}} CH_3\overset{H}{\underset{H}{C}}{-}NH_2$$

Acetonitrile or Methyl cyanide Ethyl amine

3. Another method of preparing primary amines involves the reduction of nitroparaffins. This method is becoming increasingly important, since the nitroparaffins are being produced commercially in large quantities by Commercial Solvents Corporation.

$$\underset{\text{Nitromethane}}{CH_3NO_2} + 6[H] \rightarrow \underset{\text{Methyl amine}}{CH_3NH_2} + 2\,H_2O$$

4. Primary amines can be prepared by the direct reaction of ammonia on an alkyl halide. From a theoretical viewpoint, this would appear to be the most convenient method of preparing primary amines. However, the reaction yields a mixture of primary, secondary, tertiary amines and quaternary salts (see page 298). Various chemical or physical means are used for separating these end products, the exact method depending upon the compound desired.

Physical Properties of Primary Amines.—The first two members of the series of primary amines are gases at ordinary temperatures; the middle members are liquids; and those containing more than 12 carbon atoms are solids.

Methyl amine and ethyl amine both are soluble in water. They have an ammoniacal odor.

Reactions of Amines.—1. *Combination with water.* In line with the concept of amines as substituted ammonia, the amines dissolve in water to give alkaline solutions, and unite with acids to form salts. It is a familiar fact that ammonia dissolves in water to give an alkaline solution. Similarly, methyl amine, in common with the other amines, combines with water to give an hydroxyl derivative that ionizes to give an alkaline solution.

$$\underset{\substack{\text{Methyl}\\ \text{amine}}}{CH_3NH_2} + H_2O \rightarrow \underset{\substack{\text{Methyl ammonium}\\ \text{hydroxide}}}{CH_3NH_3OH}$$

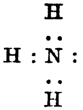
Methyl ammonium hydroxide is a stronger base than ammonium hydroxide.

2. *Reaction with acids.* Another characteristic reaction of the primary amines, as well as of ammonia, is the formation of salts with both organic and inorganic acids.

$$\underset{\substack{\text{Methyl}\\ \text{amine}}}{CH_3NH_2} + HCl \rightarrow \underset{\substack{\text{Methyl amine}\\ \text{hydrochloride}}}{CH_3NH_2 \cdot HCl}$$

Thus, by treatment with hydrochloric acid or nitric acid, amines that are insoluble in water can be brought into solution. The free amines can be regenerated from their salts by the action of a strong base, such as sodium hydroxide.

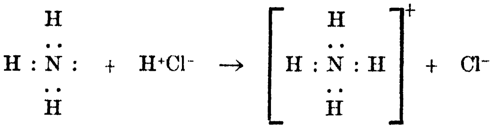
In order to understand the theoretical basis for salt formation by the amines, it is necessary to consider the electronic structure of the nitrogen atom. For simplicity, let us first consider the case of ammonia.



$$\begin{array}{ccc} & H & \\ & \cdot\cdot & \\ H: & N & : \\ & \cdot\cdot & \\ & H & \end{array}$$

(Note: Dots represent electrons in the outer electron shells of the atoms)

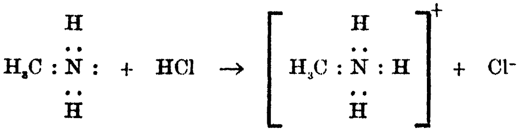
The nitrogen atom has a complete octet of valence electrons, but it still is capable of holding additional atoms or groups, because it has a pair of unshared electrons. These unshared electrons are termed "lone pairs." When ammonia reacts with acids, the proton (i.e., hydrogen ion) of the acid joins to the nitrogen atom, the full combining power of the nitrogen atom is satisfied, and the NH_4 group formed has acquired a positive charge.



$$\begin{array}{ccc} & H & \\ & \cdot\cdot & \\ H: & N & : \\ & \cdot\cdot & \\ & H & \end{array} + H^+Cl^- \rightarrow \left[\begin{array}{ccc} & H & \\ & \cdot\cdot & \\ H: & N & :H \\ & \cdot\cdot & \\ & H & \end{array}\right]^+ + Cl^-$$

Hence, in aqueous solution, the two ions, NH_4^+ and Cl^-, are formed.

The reaction of methyl amine with hydrochloric acid to form a salt is analogous to the reaction of ammonia with the same acid.



$$\begin{array}{ccc} & H & \\ & \cdot\cdot & \\ H_3C: & N & : \\ & \cdot\cdot & \\ & H & \end{array} + HCl \rightarrow \left[\begin{array}{ccc} & H & \\ & \cdot\cdot & \\ H_3C: & N & :H \\ & \cdot\cdot & \\ & H & \end{array}\right]^+ + Cl^-$$

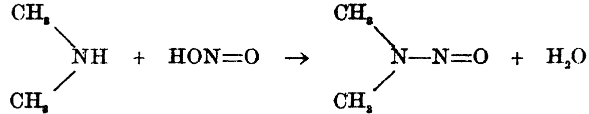
The four groups or atoms around the nitrogen atom are held by covalent bonds, but the fifth group found in this type of compound (the Cl^-, in this case) is held by electrostatic attraction.

The reaction of amines with nitrous acid can be used to distinguish the different classes of amine. With primary amines, nitrous acid yields a primary alcohol and gaseous nitrogen.

$$\underset{\text{Methyl amine}}{CH_3NH_2} + \underset{\text{Nitrous acid}}{O{=}NOH} \rightarrow \underset{\text{Nitrogen}}{N_2\uparrow} + H_2O + \underset{\text{Methyl alcohol}}{CH_3OH}$$

This type of reaction is used in the determination of amino groups (—NH_2) in proteins by the Van Slyke method (see page 561).

Treatment of secondary amines with nitrous acid yields a nitroso compound.

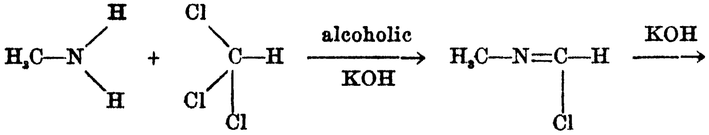


Dimethyl amine A nitroso compound

The nitroso compounds are usually a green or yellow color, and are insoluble in water. These properties are useful in the recognition and identification of the nitroso compounds.

Tertiary amines do not react with nitrous acid to give stable derivatives.

3. *Carbylamine reaction.* Primary amines form compounds known as carbylamines when they react with chloroform and alcoholic potassium hydroxide. The formation of a carbylamine is used as a test for primary amines because of its characteristic and disagreeable odor. Since secondary and tertiary amines do not react in this manner, this reaction is a sensitive test for primary amines.



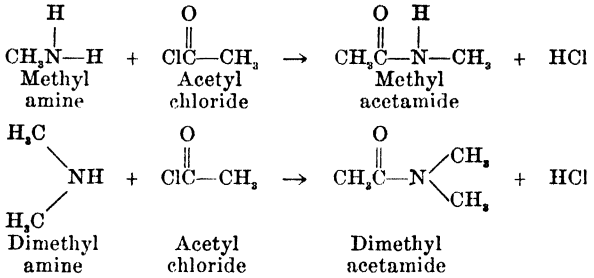
Methyl amine Chloroform

$$\underset{\text{Methyl isocyanide or methyl carbylamine}}{H_3C{-}N{=}C^{*}} + KCl + H_2O$$

---

*The student will note this exception to the usual quadrivalence of carbon. The evidence at the present time favors the existence of divalent carbon in this compound.

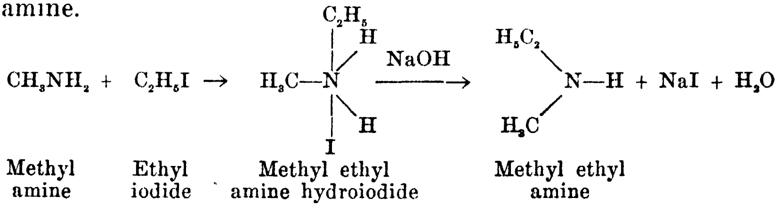
4. *Reaction with acyl halides.* Primary and secondary amines react with acyl halides to form substituted amides.



The compounds formed in these reactions are unusual in that they combine the structures of both amines and amides.

Tertiary amines contain no replaceable hydrogen on the nitrogen atom and, accordingly, cannot form derivatives of this type.

Preparation of Secondary Amines.—Secondary amines can be prepared by the reaction of an alkyl halide with a primary amine.



Other special procedures for the preparation of secondary amines also are used.

Tertiary Amines.—Tertiary amines can be prepared by treating ammonia with an excess of an alkyl halide. The free amine then is liberated by the action of sodium hydroxide.

$$\underset{\text{Methyl iodide}}{3\ CH_3I} + NH_3 \rightarrow \underset{\text{Trimethylamine}}{(CH_3)_3N} + 3\ HI$$

A more convenient and less expensive method of preparing trimethylamine involves heating a mixture of formalin and ammonia to 110° C. in a closed vessel.

$$\underset{\text{Formaldehyde}}{9\ HCHO} + 2\ NH_3 \xrightarrow{110^\circ\ C.} \underset{\text{Trimethylamine}}{2\ (CH_3)_3N} + 3\ CO_2 + 3\ H_2O$$

Trimethylamine is distributed more widely in natural products than are the other methyl amines. It is present in herring brine in considerable quantities. Trimethylamine also can be obtained from beet sugar molasses by the decomposition of betaine. Trimethylamine is present in the spores of *Tilletia levis*, the "stinking smut" of wheat. The odor of trimethylamine, especially when it is diluted, is very repulsive. It is fishlike, and clings tenaciously to clothing.

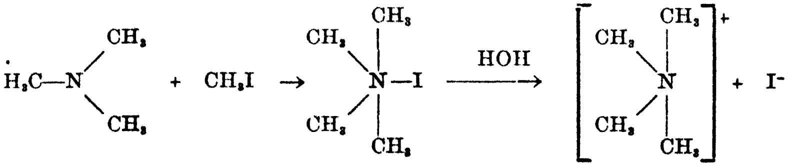
The tertiary amines contain no replaceable hydrogens; thus, they do not give many of the reactions characteristic of primary and secondary amines.

Uses of Amines.—The amines are basic substances; consequently, they will react with fatty acids to form organic soaps. These soaps dissolve readily in mineral and vegetable oils. Satisfactory emulsions can be prepared by adding a mixture of organic soap and oil to water. Triethanolamine $(HOCH_2CH_2)_3N$, soaps are used in mineral oil emulsions for orchard sprays. Because of their low alkalinity, foliage damage is slight.

A 1 M aqueous solution of monoamylamine has a pH 11.67, compared to pH 11.62 for ammonium hydroxide of the same concentration.

Triamylamine, $(C_5H_{11})_3N$, has been found to be effective as an inhibitor of acid corrosion of metals. In one investigation it was found that 0.13 per cent of n-triamylamine in 1 N sulfuric acid reduced the corrosion of steel exposed to the acid solution by 99 per cent.

Tetraalkyl Salts and Bases.—Tetraalkyl ammonium salts are formed by the action of an excess of alkyl halide on ammonia.



Trimethylamine

Tetramethylammonium iodide
(a quaternary salt)

They also can be prepared by the action of alkyl halides on a tertiary amine. These compounds are known as *quaternary salts.* The quaternary salts are stable solids, and resemble the corresponding ammonium salts.

When tetraalkyl chlorides are heated, a tertiary amine and an alkyl chloride are obtained.

$$\underset{\text{Triethylmethyl-ammonium chloride}}{(C_2H_5)_3(CH_3)N.Cl} \xrightarrow[\Delta]{} \underset{\text{Triethyl-amine}}{(C_2H_5)_3N} + \underset{\text{Methyl chloride}}{CH_3Cl}$$

The importance of this reaction is that the alkyl chloride liberated always contains the *smallest alkyl group* that was attached to the nitrogen in the quaternary salt. This reaction has proved very useful in the investigation of alkaloids and other nitrogenous compounds.

Quaternary ammonium salts in which all four alkyl radicals are different can be resolved into optically active forms. The nitrogen atom is comparable to the asymmetric carbon atom in the optically active compounds discussed previously. It is assumed that the four different groups are arranged in space to form a tetrahedron around the nitrogen atom.

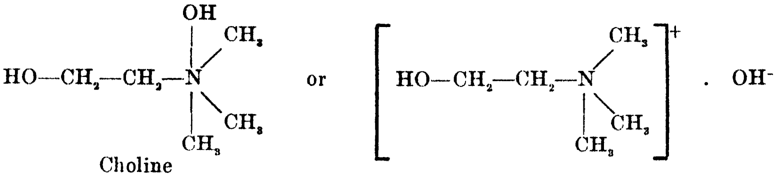
Hyamine 1622 is the trade name of a quarternary ammonium compound that is a powerful deodorant and bactericide. It can be used to destroy such powerful odors as those from garlic, onions, garbage, and decayed fish. As a bactericide it is 200 times as effective as carbolic acid. Its solutions are stable and when properly diluted are harmless to man and animals.

Quaternary ammonium hydroxides can be prepared from the quaternary salts by the action of silver hydroxide in the presence of alcoholic potassium hydroxide.

$$\underset{\text{Tetramethyl-ammonium iodide}}{(CH_3)_4NI} + AgOH \xrightarrow[KOH]{\text{alcohol}} \underset{\text{Tetramethyl-ammonium hydroxide}}{(CH_3)_4NOH} + AgI$$

The quaternary ammonium hydroxides are crystalline solids. When dissolved in water, they are strong bases, comparable to sodium and potassium hydroxide.

Choline.—The structural formula assigned to choline, an important quaternary base, can be represented as:

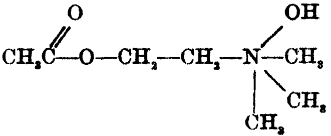


Choline

It is a constituent of the lecithins and the sphingomyelins. If experimental animals are fed a diet high in fat and deficient in choline (phospholipids, etc.), an abnormally large quantity of fat is deposited in the liver. Experiments have shown that the addition of choline to the diets of these animals will prevent this deposition of fat in the liver. An explanation of the action of the choline in preventing fat from accumulating in the liver is that choline is needed to form lecithins, which are believed by Bloor and others to act as "transport agents" for the removal of the fatty acids from the liver. More experiments are needed, however, to confirm this hypothesis.

Choline sometimes is considered to be one of the water-soluble vitamins (see page 718).

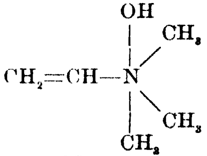
Acetylcholine.—The acetyl derivative of choline has been shown to be involved in the transmission of nerve impulses.



Acetylcholine

Acetylcholine, then, can be thought of as the chemical messenger of the nerve impulse of certain nerves. The role of acetylcholine is brought out strikingly by the following words of Dale, who has done much work on the chemistry involved in the transmission of nerve impulses: "As I speak to you, I have every reason to suppose that the muscle fibers of my tongue and my jaws are being activated by innumerable little charges of acetylcholine, fired at them, as it were, from the endings of the nerve fibers."

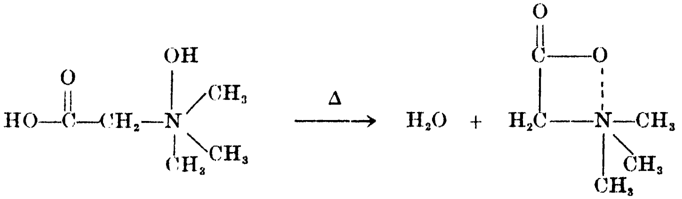
Neurine.—When choline undergoes putrefaction by bacteria, dehydration of the ethanol side chain occurs, and neurine is formed.



Neurine
(vinyltrimethylammonium hydroxide)

Unlike choline, which is not toxic, neurine is exceedingly poisonous. It can occur among the putrefactive decomposition products of meat and fish.

Betaines.—The betaines (pronounced bē'tȧ ēns) are a group of basic quaternary salts formed in plants. The simplest member of the series, known just as betaine, can be considered as an oxidation product of choline. It crystallizes as the hydroxide (A), but readily loses water upon heating to form an internal salt probably of the structure shown in (B).



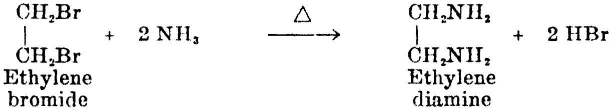
Betaine (A) Betaine (B)

Betaine hydrochloride (Acidol) is used in the treatment of hypoacidity. It yields 24 per cent HCl, and is a convenient means of administering HCl. Young sugar beets may contain as much as 2.5 per cent of betaines.

Diamines

The diamines differ from the compounds we have been considering in that they contain two amino groups instead of only one. The diamines are similar to the monoamines in their properties and in the methods used for their preparation.

Ethylenediamine can be prepared by heating alcoholic ammonia with ethylene bromide.



$$\underset{\substack{\text{Ethylene}\\ \text{bromide}}}{\begin{matrix} CH_2Br \\ | \\ CH_2Br \end{matrix}} + 2\,NH_3 \xrightarrow{\Delta} \underset{\substack{\text{Ethylene}\\ \text{diamine}}}{\begin{matrix} CH_2NH_2 \\ | \\ CH_2NH_2 \end{matrix}} + 2\,HBr$$

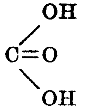
Putrescine (tetramethylenediamine), $NH_2—CH_2—CH_2—CH_2—CH_2—NH_2$, is one of the putrefactive decomposition products of meat. It is formed from the amino acid, arginine.

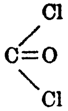
Cadaverine (pentamethylenediamine), $NH_2(CH_2)_5NH_2$, is also a putrefactive decomposition product of proteins. It is formed from the amino acid, lysine, and was first discovered in putrefying human cadavers; hence its name.

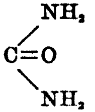
Putrescine and cadaverine originally were termed "ptomaines," and were thought to be responsible for "ptomaine poisoning." These two diamines are inert physiologically when they are taken by mouth. "Ptomaine poisoning" often has been confused with botulism, which is a type of food poisoning caused by the bacterial toxin produced by the organism *Clostridium botulinum.* This toxin is very potent; there is a case on record in which a woman opened some home-canned green beans, which had a slight "off odor." She tasted a spoonful, and, since they were not to her liking, she discarded the rest of the jar. Soon she became violently ill, and died of botulism forty-eight hours later. Botulinum toxins in canned foods result from the failure to destroy the responsible organism and its toxin by adequate heating in the canning process. Even if canned foods do contain botulinum toxins, they can be rendered nontoxic merely by boiling the food for ten minutes after the can has been opened. This treatment destroys the toxins. Odor is no criterion of the presence or the absence of botulinum toxins. Wholesome-appearing food can contain lethal doses of the poison.

Urea

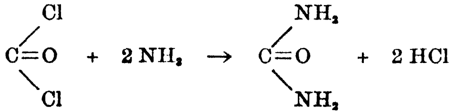
Urea is the amide of carbonic acid.


Carbonic
acid


Carbonyl chloride
(diacid chloride)


Urea
(carbamide)

The formation of urea from carbonyl chloride (phosgene) illustrates how it is related in structure to carbonic acid. Phosgene was one of the poisonous gases used in World War I.


Carbonyl chloride
(phosgene)

Urea
(carbamide)

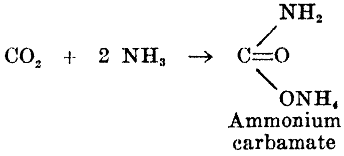
Urea is the principal end product of nitrogen metabolism in man and the higher apes. It is present in blood plasma in a concentration of from 0.02 to 0.04 per cent, and in urine to the extent of about 2.0 per cent. The normal person on an average diet excretes about 30 grams of urea per day.

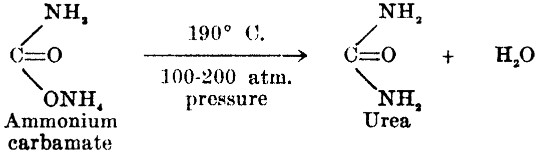
Urea is of historical interest in that it was the first admittedly organic compound to be synthesized in the laboratory from inorganic materials. Wöhler in 1828 formed urea by heating ammonium cyanate.

$$NH_4—O—C{\equiv}N \xrightarrow{\Delta} CO(NH_2)_2$$

As was mentioned earlier, compounds were classed either as inorganic or as organic because it was thought that organic compounds could be formed only by living processes. The synthesis of urea in the laboratory demonstrated that "vital forces" were not necessary for the formation of organic compounds. This was an incentive for research in the preparation of other organic compounds.

Commercially urea is produced by heating ammonia and carbon dioxide under pressure and at a temperature of 190° C. Ammonium carbamate probably is formed first and decomposes into urea and water.



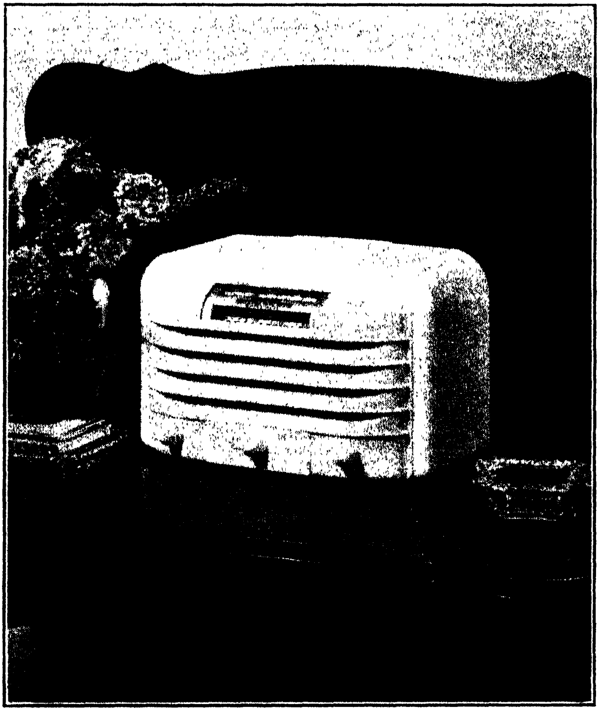


Urea also is made commercially by the hydrolysis of cyanamide.

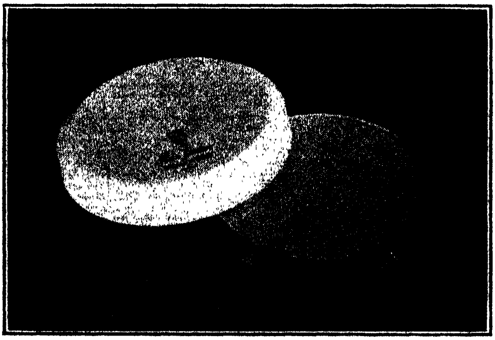
$$\underset{\text{Cyanamide}}{H_2N\text{—}CN} + H_2O \rightarrow \underset{\text{Urea}}{CO(NH_2)_2}$$

Urea is a white, crystalline compound, very soluble in water, quite soluble in alcohol, but insoluble in ether. Since it is an important article of commerce, it now is available in carload lots. Urea is used as a high-grade nitrogen fertilizer. A urea-formaldehyde fertilizer, called *uroform,* recently has been announced by the U. S. Department of Agriculture. The ratio of the two components can be adjusted so that the nitrogen becomes available at various rates depending on crop requirements. Another commercial preparation is *Ual,* a urea-ammonia liquor.

Large quantities of urea are used in the manufacture of plastics. Under the influence of heat and in the presence of catalysts, urea reacts with formaldehyde to form polymerized products that can be molded at high temperatures and pressures. These urea resins are used for such articles as radio cabinets, electric switch plugs and plates, shades and reflectors for lighting fixtures, buttons, cosmetic containers, and decorative fittings for household appliances. Urea resins are valuable for the manufacture of molded products because they show such distinc-

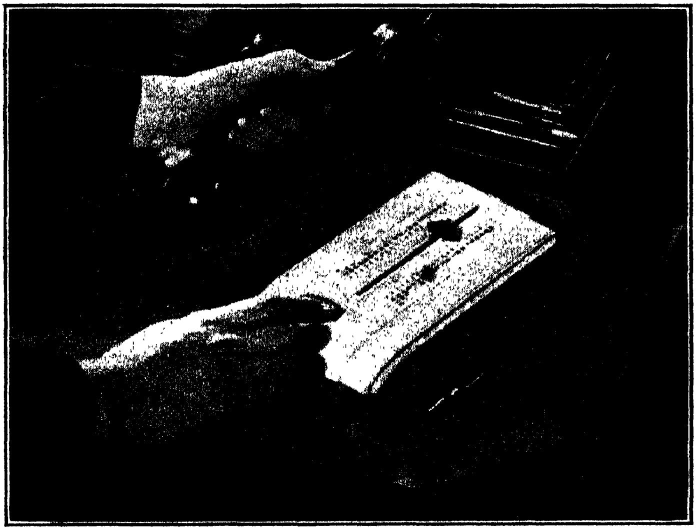


A.

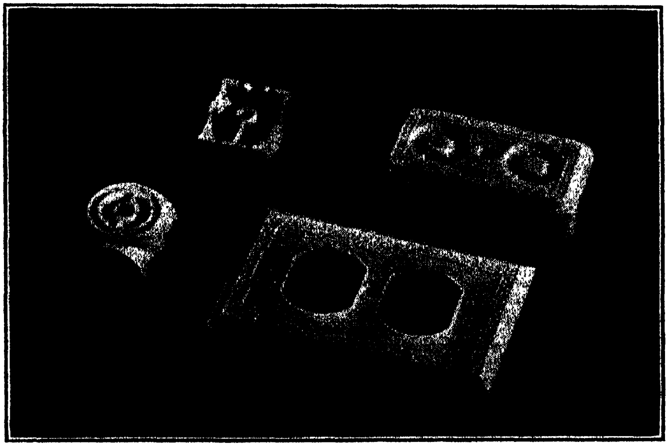


B.

Fig. 42.—Articles made from urea-formaldehyde resins. *A*, A radio cabinet with knobs to match. *B*, Attractive sanitary cosmetic containers can be made from this type of resin. *C*, Telephone indices are molded from light-colored urea resins. *D*, Urea-molding materials are used to good advantage in electric switch plugs and plates since they combine attractiveness with electric insulating qualities. (Courtesy of the Bakelite Corporation.)



C.



D.

tive advantages as freedom from odor and taste, availability in a wide range of translucent and opaque colors, and excellent light diffusion properties.

Urea-formaldehyde resins that have not been polymerized to form such large molecules as those in molded products are used as glues for plywood and veneer on furniture. By one of the new processes the urea-formaldehyde glue is worked into a foam. The glue can be used with thin veneers without causing wrinkles because it is thus possible to apply a very thin coat of glue.

In combination with alkyd resins urea-formaldehyde resins produced enamels that are resistant to alcohol, grease, and fruit acids.

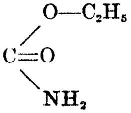
Urea now is being used as a seasoning agent to reduce checking, splitting, and similar losses that occur in the air or kiln drying of lumber. No disadvantage results from the use of urea for this purpose since urea is stable, nontoxic to the skin, and does not corrode tools that are employed for dressing the lumber. Urea-treated wood is said to be less susceptible to attack by fungi and rot than are untreated woods.

Under the stress of war conditions cheap substitutes were sought for the expensive protein in the feed of livestock. Experiments have shown that urea could serve as a substitute for as much as one-third of the protein nitrogen in the rations. When this amount of urea was added to the diet, there was no noticeable decrease in the quality of the milk of dairy cows, and no failure to gain weight by beef cattle provided the diet was properly balanced.

An interesting application of urea to medicine is its use in the treatment of infected deep wounds. In World War I badly wounded soldiers who could not be removed from the battlefield for a day or two often were found to have maggots in their wounds. Their recovery was very surprising. Later it was found that deep wounds that failed to heal quickly responded to treatment when maggots were put into them. An improvement of this technique was the growing of the maggots under antiseptic conditions. Later research showed that the effective curative reagent was the urea in the excreta of the maggots, so that now urea is employed in treating slowly healing wounds without the unpleasant association of the maggots. A 2 per cent solution of urea is said to be effective as a gargle for sore throat. Thiourea, $H_2N\text{-}CS\text{-}NH_2$, the sulfur analog of urea, when applied in 5 per cent aqueous solution as a momentary dip has been found effective in controlling decay of oranges.

Urethane

Carbamic acid, $HO\text{-}CO\text{-}NH_2$, is not known in the form of the free acid, but only as its salts and esters. The ethyl ester is called *urethane.*

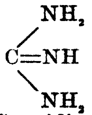


Urethane

Preliminary results indicate that urethane has a definite palliative effect in the treatment of dreaded leukemia, a blood disease for which there is no known cure.

Guanidine

From a structural viewpoint guanidine can be considered as urea in which the oxygen atom of the urea has been replaced by the imino (=NH) group.

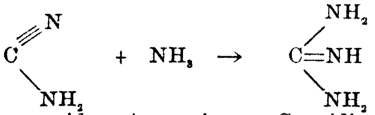


Guanidine

Guanidine gets its name from guanine, one of the purine bases, from which it was first isolated as a decomposition product. It is a rather common practice in organic chemistry to name a substance derived from another compound by dropping the final *e* or *ne* in the name of the parent compound, and adding *dine* to form the name of the derivative. Guanidine illustrates this practice.

The principal importance of guanidine from our viewpoint is its occurrence as a part of the molecule of arginine, one of the amino acids. It also is a part of the molecules of creatine and creatinine, both of which are of physiological importance. Guanidine is found in sugar beets, where, as a water-soluble component, it passes into the molasses in the process of sugar manufacture.

Preparation of Guanidine.—Guanidine can be prepared by the addition of ammonia to cyanamide.

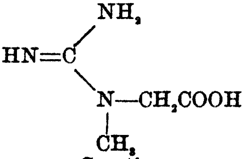

Cyanamide Ammonia Guanidine

Properties.—Guanidine is a colorless, crystalline, hygroscopic solid, which is soluble in water and alcohol. It is a strong base and absorbs carbon dioxide from the air. Witzemann found that the reactions of glucose in the presence of guanidine were similar to the reactions taking place in the presence of sodium hydroxide and potassium hydroxide.

The nitric acid and the picric acid salts of guanidine are sparingly soluble and can be used for identification purposes.

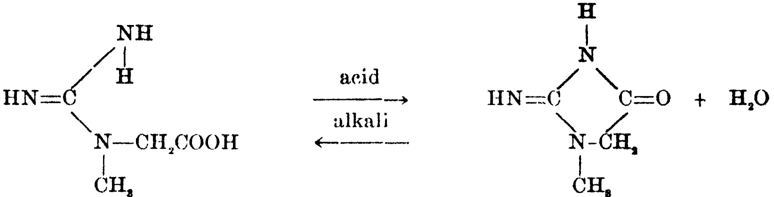
Creatine and Creatinine

Creatine (methylguanidine-acetic acid) is distributed widely in animal tissues, being present most abundantly in muscles, where it plays an important role in muscle contraction. Its structure can be represented as:


Creatine

An adult human body has been estimated to contain about 100 grams of creatine, the largest part of which is present in the muscles.

When creatine is heated in acid solution, it is transformed into creatinine. The reverse change takes place in alkaline solution to give a salt of creatine.



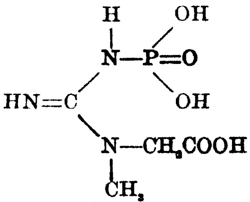
Creatine Creatinine

In 0.5 N hydrochloric acid at a temperature of 117° C., the change from creatine to creatinine is complete in about fifteen minutes.

Creatinine, the inner anhydride of creatine, occurs normally in the urine. From 1 to 2 grams are excreted daily by the average adult. As was shown by Folin, the amount of creatinine excreted is not readily influenced by the amount of protein in the diet or the amount of muscular work.

Creatine Phosphate

The isolation of creatine phosphate (phosphocreatine) from muscle was reported by Fiske and Subbarow at approximately the same time the Eggletons isolated the same compound and named it phosphagen. The formula can be represented as follows:



Creatine phosphate

Eggleton estimated that 80 per cent of the creatine in resting muscle is present as phosphagen. The stimulation of muscle causes, among other things, the hydrolysis of creatine phosphate to creatine and phosphoric acid, liberating 120 calories per gram of phosphoric acid formed.

Study Questions

1. Diagram type formulas for primary, secondary, and tertiary amines.
2. What is the Hofmann reaction? Show equations for the preparation of ethyl amine using this reaction.
3. Why is it not practical to prepare primary amines by the direct reaction of ammonia and an alkyl halide?
4. How do primary amines resemble ammonia in chemical reactions?
5. Explain the electronic structure of the nitrogen atom that makes possible salt formation by primary amines.
6. How can the reaction of amines with nitrous acid be used to distinguish between primary, secondary, and tertiary amines?
7. What is a sensitive test for primary amines?
8. Write an equation for the formation of substituted amines by the reaction of acetyl chloride with a primary and also a secondary amine. Why is not this type of reaction possible between a tertiary amine and an acyl halide?
9. What is the formula for trimethylamine? What are some natural sources of this amine? What distinctive physical property does it possess?
10. Write the formula for a quaternary salt, and give the equation for its formation.
11. What types of product are obtained when quaternary salts are heated? Of what significance is this reaction?
12. Under what conditions are quaternary salts optically active?
13. How do the diamines differ in structure from primary, secondary, and tertiary amines?
14. Give formulas for diamines occurring in the putrefactive decomposition products of proteins.
15. What is botulism? What precautions can be taken with home-canned foods to prevent any danger of botulism?
16. By means of structural formulas show the relationship in structure of carbonic acid, phosgene, and urea.
17. Of what physiological importance is urea?
18. How was urea first synthesized? What theory accepted up until that time was disproved by its synthesis?
19. Write the equation for the formation of urea from carbon dioxide, water, and ammonia.
20. What are five or six uses for urea?
21. Why were maggots effective as an aid in the healing of infected deep wounds in World War I?
22. What is a use of calcium cyanamide?
23. How is guanidine related to urea in structure?
24. What is the physiological importance of creatine and creatinine? Write an equation for the interconversion of the two products.

25. From what source was creatine phosphate first isolated? What role does this compound play in muscle contraction?
26. What is the probable action of choline in the liver? What is the structural formula of choline? Of acetylcholine?
27. How is neurine related to choline?
28. What are betaines and where do they occur?

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CHAPTER XIV

SUGARS

Introduction.—The sugars are a group of similar compounds belonging to a larger class of substances known as carbohydrates. Carbohydrates are the principal energy-giving foods for both plants and animals. The interrelationship of the compounds that will be discussed in this chapter and in the following chapter is shown by the accompanying outline.

The term *carbohydrate* originated from the early observations that certain compounds composed of carbon, hydrogen, and oxygen contained hydrogen and oxygen in the proportions of two to one; that is, in the same ratio as in water. Moreover, these compounds, when heated in the dry state, decomposed to give carbon and water. These observations gave rise to the early designation of such compounds as "hydrates of carbon," or carbohydrates. However, later observations showed that there were a number of compounds containing hydrogen and oxygen in the proportion of two to one that could not be classed as carbohydrates as, for example, lactic acid, $C_3H_6O_3$. Also, there are compounds that belong to the class of carbohydrates that do not contain hydrogen and oxygen in the same proportion as in water—for example, rhamnose, $C_6H_{12}O_5$. Thus the term carbohydrate is somewhat of a misnomer, but because it is generally understood, it continues to be used.

Carbohydrates can be defined as *polyhydroxy aldehydes or ketones, or compounds that yield these on hydrolysis.* The significance of the definition will become clear as the formulas for the various carbohydrates are discussed.

Monosaccharides

We shall begin our discussion of the sugars with the simplest class, called the monosaccharides. These sugars contain but one aldehyde or ketone group. They cannot be broken down by hydrolysis to yield more than one sugar, as can the disaccharides and the trisaccharides, which will be discussed later.

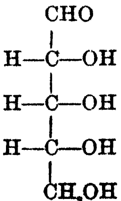
atom written to the right. The L- sugars always have the hydroxyl group on the lowest asymmetric carbon atom written to the left. In dihydroxyacetone there is no asymmetric carbon atom, and no stereoisomer is possible.

Tetroses.—There are six tetroses. Two are ketose sugars and the others are aldoses. Not all the D-tetroses rotate plane polarized light to the right, as might be expected from the name, nor are all the L-tetroses levorotatory. The attempt to classify sugars according to their actual effect on plane polarized light leads to a great deal of confusion; so, instead, the D-designation indicates that the compound is related to D-glyceric aldehyde with the hydroxyl on the bottom asymmetric carbon atom written to the right, and L- sugars are related to L-glyceric aldehyde with the hydroxyl written to the left.

The student will save himself much confusion in studying the structure of sugars if he keeps the concept clearly in mind that the letters D- and L- placed before the name of a sugar are not abbreviations of dextro and levo. They have no relation whatsoever to the optical rotation of a sugar. Any case in which a D-sugar is dextrorotatory is purely fortuitous. Instead of indicating the direction of rotation, the letters D- and L- signify that the particular sugar belongs to the D- or L- family of sugars, which can be considered as having been built up from D- or L-glyceric aldehyde.

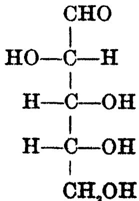
It is unfortunate that such a system was ever introduced, but it has been used so widely in the accumulated literature on carbohydrates that a change to a more logical system would cause even more confusion.

Pentoses.—The four D-aldopentoses are:



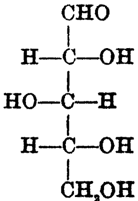
$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

D-Ribose



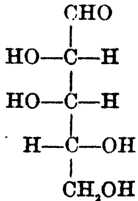
$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

D-Arabinose



$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

D-Xylose



$$\begin{array}{c}\mathrm{CHO}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{HO{-}C{-}H}\\ |\\ \mathrm{H{-}C{-}OH}\\ |\\ \mathrm{CH_2OH}\end{array}$$

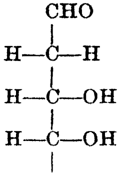
D-Lyxose

The pentoses rarely occur free in nature, but more frequently are encountered in the form of pentosans, which are made up of many pentose molecules. Pentoses can be obtained from the pentosans by hydrolysis with acid.

Arabinose. Both the D- form and the L- form of arabinose are found in the combined state in nature. L-Arabinose, the most frequently encountered form, is obtained from gum arabic, cherry gum, and beet pulp by boiling with dilute sulfuric acid. In the laboratory it is prepared by the acid hydrolysis of mesquite gum. L-Arabinose is dextrorotatory. D-Arabinose has been prepared by the hydrolysis of certain glucosides.

Xylose. Xylose first was isolated from corn cobs by workers in the Department of Agriculture. Corn cobs are a good potential source of this sugar, which is used in the synthesis of vitamin C. Straw, oat hulls, cottonseed hulls, and bran also can serve as sources of L-xylose, which is dextrorotatory.

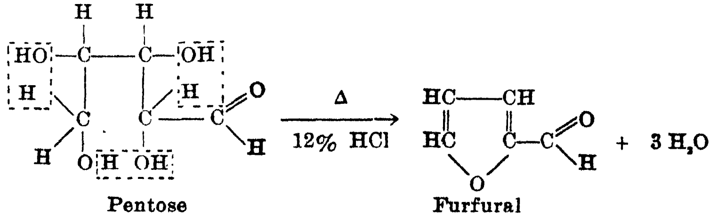
Ribose. Ribose can be thought of as an important sugar, not because of any industrial use, but because it is a constituent of nucleic acids, which are components of the chromosomes that transmit hereditary characteristics. In fact, it was first discovered in nucleic acids. A closely related compound is desoxyribose, a pentose also present in nucleic acids.



$$\begin{array}{c}
\mathrm{CHO} \\
| \\
\mathrm{H{-}C{-}H} \\
| \\
\mathrm{H{-}C{-}OH} \\
| \\
\mathrm{H{-}C{-}OH} \\
| \\
\mathrm{CH_2OH}
\end{array}$$

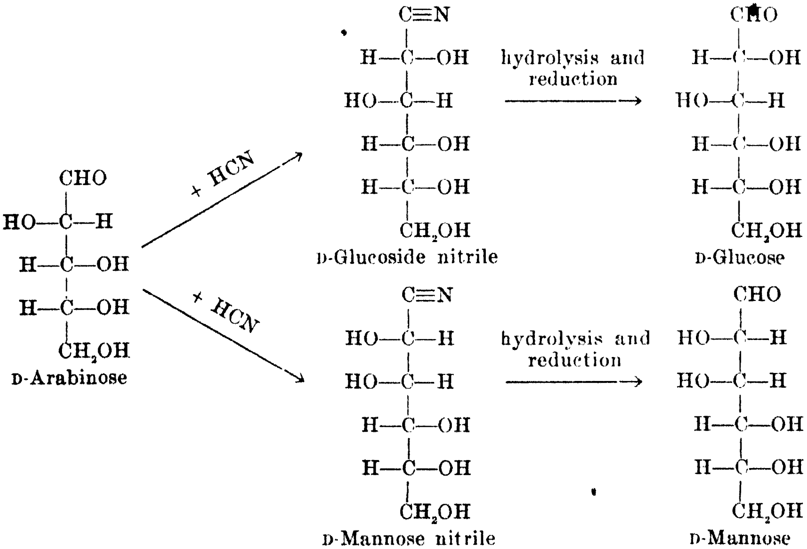
Desoxyribose

Reactions of the Pentoses. A reaction typical of the pentoses is that with 12 per cent hydrochloric acid to generate furfural.



The formation of furfural by the action of acid is used as a test for the pentoses. Often it is important to determine the amount of pentosans present in feed stuffs, such as wheat bran. The pentosan-containing material is boiled with 12 per cent hydrochloric acid, and the furfural in the distillate is precipitated quantitatively with thiobarbituric acid or phloroglucinol.

Kiliani Synthesis.—All aldose sugars react with hydrocyanic acid to form cyanohydrins. The hydrolysis of the nitrile, and the reduction of the acid to the aldehyde, yield a sugar containing one more carbon atom than the starting compound. This series of reactions is known as Kiliani's synthesis. The reaction is given for the pentoses because it will illustrate the formation of aldoses with one more carbon atom; namely, the hexoses.



Since the law of probability operates in this equation, there is just as much chance of having the hydroxyl group formed on one side of the second carbon in the nitrile compound as on the other; accordingly, there will be two configurations for the cyanohydrins. Two hexoses, therefore, result from the reaction of a pentose with hydrocyanic acid.

The other reactions of the sugars, including pentoses, will be discussed for D-glucose, the most widely distributed monosaccharide.

It seems likely that the pentoses in plants are formed from hexose uronic acids; hence, this aspect of pentose chemistry will be deferred until the uronic acids are considered.

One function of pentoses is to increase the water-retaining powers of plants. They are present in the form of gummy, gelatinous substances that retain water tenaciously. The content of pentosans in cacti and other desert plants is especially high. Those who may have noted how long one of the cacti, prickly pear, remains green even when it is removed from soil will appreciate the effectiveness of this water retention by pentosans.

Hexoses.—The hexoses are the most important class of monosaccharides. Of these, glucose is pre-eminently important and will be dealt with in some detail. Many of its reactions are given by all the sugars.

Glucose.—Glucose occurs in the free state in many fruits. Ripe grapes, for example, contain 20 to 30 per cent of this hexose; hence the name ''grape sugar'' sometimes is given to glucose. Because it is dextrorotatory, it also is called dextrose. Glucose occurs normally in the blood stream to the extent of 0.08 to 0.15 per cent. It is excreted in the urine if the disease *diabetes mellitus* is uncontrolled. As will be seen later, the metabolism of carbohydrates in the human body is largely the metabolism of glucose, because the other hexoses found in foodstuffs are converted to glucose in the body.

Commercially, glucose is prepared by the hydrolysis of starch with dilute acid. In the United States cornstarch is used as the source of dextrose, but in Europe it is manufactured from potato starch.

Chemical Structure of Glucose.—Up to this point in the discussion of carbohydrates we have assumed the formulas given for the various sugars to be correct without advancing any evidence to justify them. We shall now stop to consider some of the lines of reasoning advanced for the structural formula of glucose. This procedure is applicable to the other sugars as well.

1. A quantitative analysis for carbon, hydrogen, and oxygen, and a molecular weight determination demonstrate that the molecular formula is $C_6H_{12}O_6$.

2. Reduction of glucose with hydriodic acid gives a derivative of normal hexane, which shows that the carbon atoms in glucose are in a straight chain.

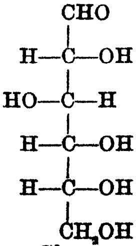
3. Glucose reacts with hydroxylamine to form a mono-oxime, which shows that glucose contains only one aldehyde or ketone group.

4. Mild oxidation of glucose yields a six-carbon atom monocarboxylic acid (gluconic acid). This shows that glucose contains an *aldehyde* group at one end of the chain.

5. Oxidation of the monocarboxylic acid gives a six-carbon atom dicarboxylic acid, saccharic acid. This result indicates that there is a primary alcohol group at the opposite end of the chain from the aldehyde group.

6. Acetyl chloride reacts with glucose to yield a penta-acetyl derivative. This demonstrates the presence of five hydroxyl groups in the molecule.

On the basis of these results and others we can write the structural formula for D-glucose as:



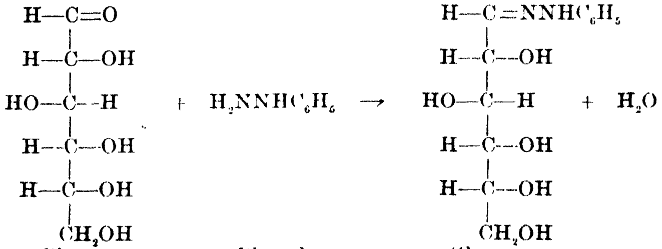
$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H—C—OH} \\ | \\ \mathrm{HO—C—H} \\ | \\ \mathrm{H—C—OH} \\ | \\ \mathrm{H—C—OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

D-Glucose

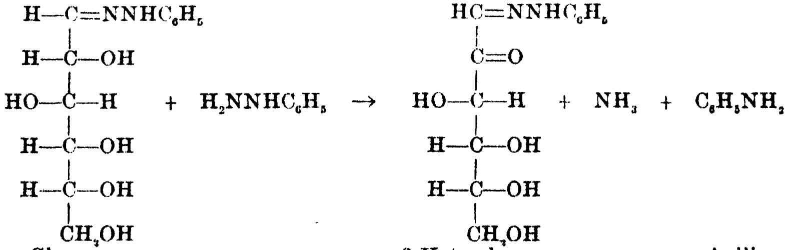
The evidence that has been presented does not give us the configuration of the molecule—that is, the spatial relationships of the hydrogens and the hydroxyls, but this can be proved by another line of reasoning. The structural formula for glucose that shows its configuration is the one we shall use in discussing the reactions of glucose. It is, therefore, preferable to use this formula of glucose from the beginning.

Chemical Reactions of Glucose.—The chemical reactions undergone by glucose are typical for most of the sugars; therefore, they are the only ones that will be dealt with in detail in our discussion of sugars.

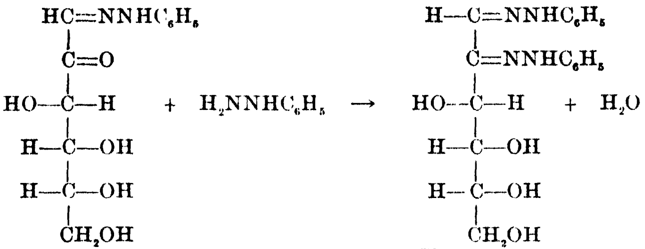
1. The formation of an osazone by the reaction with phenylhydrazine shows the presence of the aldehyde group in glucose, and is also a useful reaction for characterizing glucose and the other sugars. The first step in the reaction is the formation of a hydrazone. The hydrazones of all the sugars except mannose are soluble in water; hence, with the exception of mannose hydrazone, they are not useful for identification purposes. After the formation of the hydrazone, the excess of phenylhydrazine acts as a mild oxidizing agent, and converts the alcohol group on carbon atom number two to a carbonyl group. The carbonyl group thus formed then reacts with another molecule of phenylhydrazine to form the osazone.



D-Glucose Phenylhydrazine Glucose hydrazone



Glucose hydrazone 2-Keto-glucose hydrazone Aniline



2-Keto-glucose hydrazone

Glucosazone

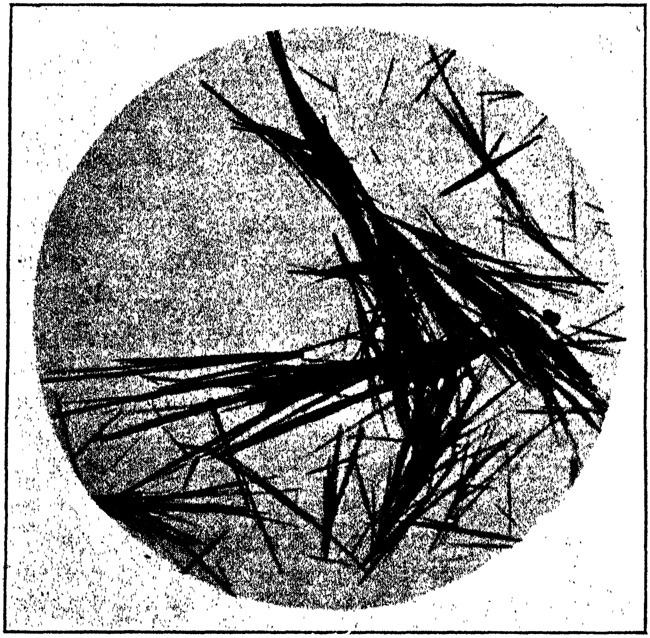
The osazones are much used in the identification of sugars for several reasons. (a) They have a characteristic crystalline form, which can be observed under the microscope. (b) The time of formation of the osazones is different for the various sugars. (c) The osazones are highly colored (brilliant green or bright yellow), and when purified have definite melting points.

2. In common with other aldehydes, glucose is oxidized easily. One of the commonly used reagents is Fehling's solution. This reagent is prepared just before use by mixing equal volumes of two solutions that we shall call A and B. Solution A contains about 7 per cent copper sulfate, and solution B is about 10 per cent sodium hydroxide and 34 per cent Rochelle salt (sodium potassium tartrate). The purpose of the tartrate is to form a soluble complex with the copper hydroxide resulting from the reaction of the sodium hydroxide and the copper sulfate. In the absence of tartrate the blue gelatinous precipitate that would be formed would turn black on heating, and thus obscure the result of the test. The alkali acts on the sugar to break it into reactive fragments.

$$\textbf{Glucose} + \textbf{Fehling's solution} \rightarrow \underset{\substack{\textbf{Cuprous oxide,}\\ \textbf{a bright red precipitate}}}{Cu_2O\downarrow} + \textbf{Oxidation products}$$

By carrying out the reaction under carefully controlled conditions, Fehling's solution can be used for the quantitative determination of glucose or other reducing sugars. The cuprous oxide formed can be weighed and the corresponding weight of reduced sugar calculated.

Benedict's solution also is used to test for the presence of glucose. It contains sodium citrate, sodium carbonate, and copper sulfate. Benedict's solution is a milder reagent than Fehling's and is more sensitive to small quantities of sugar. For this reason, it is preferred to Fehling's for detecting glucose in urine.



A.

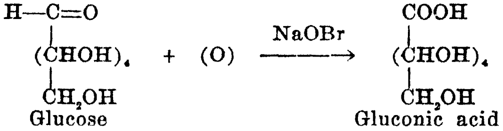
Fig. 43.—*A*, Glucosazone. *B*, Galactosazone. (Reprinted by permission. From Morrow and Sandstrom: Biochemical Laboratory Methods, John Wiley & Sons, Inc.)

When a solution containing glucose and the reagent is heated, there is a progressive change in the color of the precipitate from a greenish yellow to brick red with increasing amounts of sugar.

3. The reducing power of glucose is utilized in the silvering of mirrors.

$$\underset{}{\text{Glucose}} + \underset{\substack{\textbf{Silver}\\\textbf{hydroxide}}}{\text{AgOH}} \xrightarrow{\text{NH}_4\text{OH}} \underset{\substack{\textbf{Silver}\\\textbf{mirror}}}{\text{Ag}\downarrow} + \text{Organic acids}$$

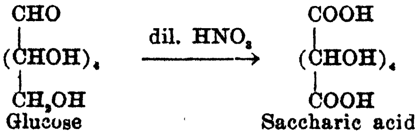
4. Glucose, on mild oxidation with sodium hypobromite, gives gluconic acid, a six-carbon monocarboxylic acid.



$$\begin{array}{c}H{-}C{=}O\\ |\\ (CHOH)_4\\ |\\ CH_2OH\\ \text{Glucose}\end{array} + (O) \xrightarrow{NaOBr} \begin{array}{c}COOH\\ |\\ (CHOH)_4\\ |\\ CH_2OH\\ \text{Gluconic acid}\end{array}$$

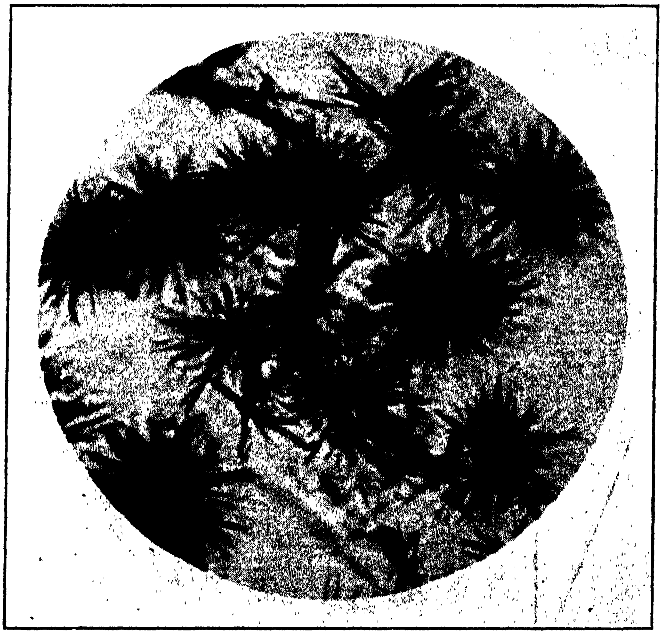
B.

5. On more vigorous oxidation glucose gives saccharic acid, a six-carbon dicarboxylic acid.



$$\begin{array}{c}CHO\\ |\\ (CHOH)_4\\ |\\ CH_2OH\\ \text{Glucose}\end{array} \xrightarrow{\text{dil. } HNO_3} \begin{array}{c}COOH\\ |\\ (CHOH)_4\\ |\\ COOH\\ \text{Saccharic acid}\end{array}$$

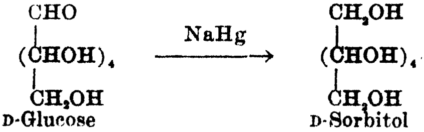
If the solution of saccharic acid is evaporated to a small volume and carefully neutralized with potassium hydroxide, crystals of the sparingly soluble monopotassium salt of saccharic acid will separate. They have a definite crystalline form that can be identified under the microscope. This procedure can be used in testing for the presence of glucose in an unknown solution.



A.

Fig. 44.—*A*, Maltosazone. *B*, Lactosazone. (Reprinted by permission. From Morrow and Sandstrom: Biochemical Laboratory Methods, John Wiley & Sons, Inc.)

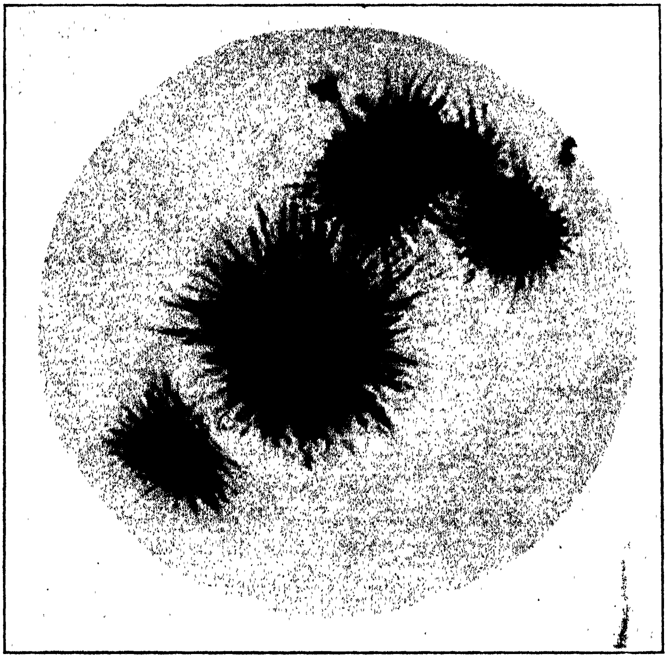
6. The aldehyde group in glucose can be reduced by means of sodium amalgam to a primary alcohol group. Sodium amalgam is prepared by grinding metallic sodium and mercury together in a mortar. It contains about 97 per cent mercury and 3 per cent sodium.



$$\begin{array}{c} CHO \\ | \\ (CHOH)_4 \\ | \\ CH_2OH \\ \text{D-Glucose} \end{array} \xrightarrow{NaHg} \begin{array}{c} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CH_2OH \\ \text{D-Sorbitol} \end{array}$$

D-Sorbitol occurs in the ripe fruit of the mountain ash. It is employed in the manufacture of synthetic ascorbic acid (vitamin C).

7. Glucose reacts with hydrocyanic acid to give a cyanohydrin from which a heptose can be obtained by methods similar to those outlined for converting arabinose into hexoses.



B.

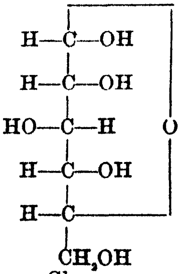
Cyclic Structure of Glucose.—There are several reactions typical of an aldehyde, such as acetaldehyde, that are not given by glucose. (a) Glucose does not form a sodium bisulfite addition product. (b) It does not decolorize fuchsine reagent. (c) In addition, the reaction with hydrocyanic acid takes place at a much slower rate, and is more difficult to bring about than with a typical aldehyde.

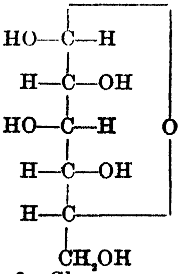
When anhydrous glucose is dissolved in a dilute solution of acetic acid and allowed to crystallize slowly at room temperature, a form of glucose separates out that has a specific rotation of +110°. This form is designated *α-D-glucose.* When its aqueous solution is allowed to stand, its specific rotation gradually changes to an equilibrium value of +52.5°. A trace of alkali will cause this change in optical rotation to take place in a few minutes.

If anhydrous glucose is dissolved in water, and glacial acetic acid is added, and the solution is heated to nearly 100° C. for a half hour or more, a form of glucose separates almost as soon as heating is stopped. This form of D-glucose has a specific rotation of +19°, and is called *β-D-glucose.* When β-D-glucose stands at room temperature, it, too, slowly changes its specific rotation to an equilibrium value of +52.5°. This phenomenon is known as mutarotation. Mutarotation can be defined as *a change in the specific rotation of a freshly dissolved sugar solution to a constant value.* This interrelationship can be represented as follows:

$$\underset{\alpha\text{-D-Glucose}}{\underbrace{+110^\circ \qquad\qquad\qquad\qquad\qquad\qquad +19^\circ}_{\substack{+52.5^\circ \\ \text{Equilibrium value}}}}\quad \beta\text{-D-Glucose}$$

To explain mutarotation, a closed-ring or hemiacetal formula for glucose was proposed, inasmuch as it allows for two modifications of D-glucose, since a fifth asymmetric carbon atom thus is introduced into the molecule.


α-D-Glucose


β-D-Glucose

As an aid to understanding we can think of the oxide ring as having been formed by the union of a hydrogen from the hydroxyl on carbon five with the carbonyl group on carbon one.

It has been postulated that the carbon atoms in the glucose molecule exist in a sort of spiral, so that the first and the fifth carbon really are close together in space. Consequently, it is easy for the hydrogen from the hydroxyl on the fifth carbon atom to combine with the carbonyl group. This type of combination is similar to that in the lactones formed by gamma and delta hydroxy acids, and also to the hemiacetals formed by the reaction between an aldehyde and an alcohol (see page 246).*

There is evidence that glucose in solution exists mainly in the form of a delta lactone. The student reasonably may wonder why, if glucose exists chiefly as the delta lactone form, it ever gives aldehyde reactions. The explanation offered is that the delta lactone forms are in equilibrium with a small but definite amount of the free aldehyde form. Thus, when a reagent is added that reacts with the aldehyde group, the equilibrium is disturbed and the lactone opens up to give more of the aldehyde form. As the aldehyde form is removed from the solution, more of the lactone form is transformed into the aldehyde form in order to maintain the equilibrium. This explains why D-glucose can react as an aldehyde. It also explains why the addition of hydrocyanic acid to glucose proceeds at a rate much slower than its addition to aldehydes such as acetaldehyde, since it is assumed that time is consumed in the transformation of the delta lactone form to the aldehyde structure.

Haworth, one of the outstanding workers in the field of carbohydrates, proposed the so-called *perspective formula* for representing the spatial configurations of the pyranose structure in sugars. There are five carbons and one oxygen united in a closed ring. In order to show the relative positions in space of the hydrogens and the hydroxyls, vertical lines are drawn at the positions of the carbon atoms in a regular hexagon. In the straight-chain formula the hydrogens and the hydroxyls that are written to the right appear at the bottom of the short vertical lines in the perspective formula. Those hydrogens and hydroxyls that are written at the left of the vertical carbon chain are placed at the top of the small lines in the perspective formula. The heavy lines in the hexagon are to convey the idea of three dimensions; hence, in viewing a perspective diagram, one should think of the plane of the ring as receding perpendicular to the plane of the page. Actually, the members of the ring are not in the same plane, but it is not possible to show this variation even in a perspective formula. Here again, as with the isomers of lactic acid, it is highly desirable to have models in order to see the three-dimensional relationships.

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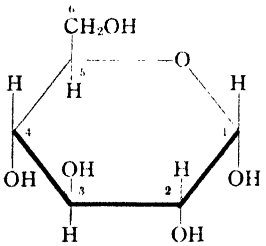
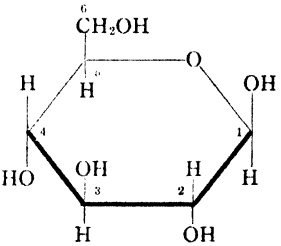
*The closed ring in glucose and many of the other sugars is described in several ways: as an amylene oxide ring, a delta lactone, or the sugar is said to possess a pyranose structure. Other ring forms may exist, such as ethylene, propylene, butylene oxide rings, and are thought to be responsible for an active form of glucose, γ-glucose.



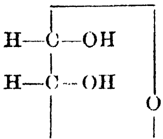
α-D-Glucose*



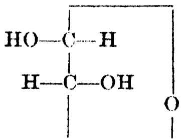
β-D-Glucose

The advantage of the perspective formulas and the reason that they are coming into common use is that they portray the idea of three-dimensional relationships better than do the older straight-chain type of formulas. The superiority of the perspective formulas in showing spatial relationships in the sugars will become evident when we examine the structural formulas for the disaccharides.

Although the matter is still somewhat controversial, especially for the ketose series of sugars, it has become the practice among chemists to write the α-modification of sugars with the hydroxyl of carbon one on the same side as the hydroxyl on carbon two, while in the β-form the hydroxyl on carbon one is written on the side opposite to the hydroxyl on carbon two.



α- Form



β- Form

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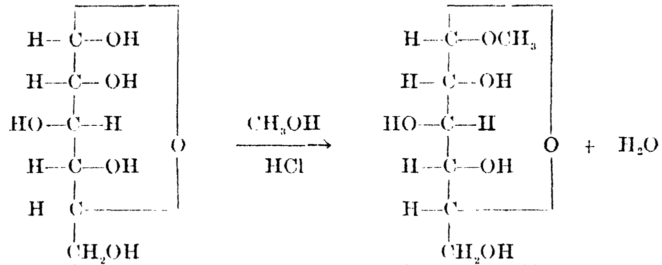
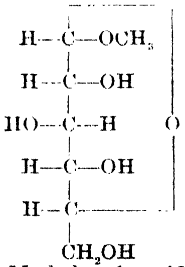
*The numbering shows the relative position of the carbon atoms as compared with their positions in the open chain or aldehyde formula for D-glucose. The carbon atom one corresponds to the carbonyl carbon atom.

Another line of evidence for the existence of glucose as a closed-ring compound is furnished by the existence of two methyl derivatives of glucose that have distinctly different properties. If α-D-glucose is dissolved in cold methyl alcohol, and the solution is saturated with dry hydrogen chloride gas, the hydrogen of the hydroxyl on the first carbon atom is replaced by a methyl group.

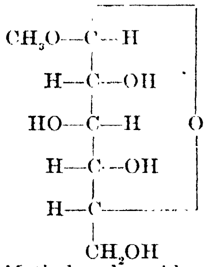


α-D-Glucose α-Methyl-D-glucoside

A compound *α-methyl-D-glucoside* results from the reaction. This is the first mention of a class of compounds called the glucosides, a type of carbohydrate that will be discussed later in more detail. If β-D-glucose is treated in the same manner as was described for α-D-glucose, a methyl derivative also is obtained. The formulas of the two methyl glucosides are shown for the sake of comparison.



α-Methyl-D-glucoside
(specific rotation = +159°)

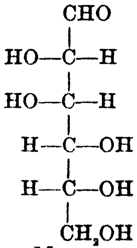


β-Methyl-D-glucoside
(specific rotation = -34°)

The two methyl glucosides exhibit wide differences in their specific rotations. The alpha form has a specific rotation of +159°, while that of the beta form is -34°. In addition to this variation in specific rotation, the two glucosides are hydrolyzed by different enzymes. α-Methyl-D-glucosides are hydrolyzed only by maltase, while β-methyl-D-glucosides are hydrolyzed by the enzyme emulsin, but not by maltase. As we shall see later, enzymes are substances formed by living cells. One of their most characteristic properties is their specificity. Their action has been compared to that of a lock and key.

Mannose.—Mannose differs from glucose only in the position of the hydroxyl group on the carbon atom adjacent to the carbonyl group. Since osazone formation affects only the first two carbon atoms, glucose and mannose form the same osazone. Mannose occurs abundantly in nature in the form of complex condensation products called mannans. Orange peel contains a small amount of free mannose. The chief source of the sugar is vegetable ivory, the endosperm of the seed of the tagua palm. Vegetable ivory is used for making buttons, such as are used on overcoats, and mannose is prepared by the acid hydrolysis of the trimmings and scraps from the button industry.

The naturally occurring dextromannose can be fermented by yeast, but the levo form cannot.



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

D-Mannose

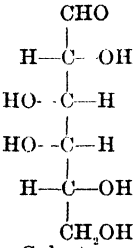
D-Mannose, on reduction with sodium amalgam, gives the hexahydric alcohol, D-mannitol. It is the most abundant naturally occurring hexahydric alcohol, and is found in pineapples, carrots, turnips, and onions. D-Mannitol is present in silage to the extent of 0.5 to 2.5 per cent, having been formed by the bacterial reduction of sugars.

D-Mannitol now is prepared industrially by the electrolytic reduction of D-glucose. Inorganic salts in the reduction mixture bring about the tautomeric change of glucose to mannose, which then is reduced to the hexahydric alcohol. When it is nitrated, mannitol forms a valuable explosive.

Galactose.—Galactose does not occur to any extent in the free state in nature, but it constitutes one-half of lactose, the sugar in milk. It is present also in plant gums and in mucilages. It is a constituent of the cerebrosides found in the brain and in nerve tissue. In the mammary gland of lactating animals, galactose is formed from glucose, and subsequently is used in the synthesis of milk sugar. It has never been possible to bring about this change from D-glucose to D-galactose *in vitro.*[*]

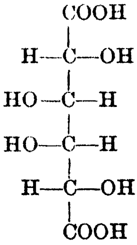
In the laboratory, galactose often is prepared by the hydrolysis of sawdust of the Western larch.

The reactions of D-galactose are, in general, the same as those given by the other aldohexoses. On oxidation with dilute nitric acid, mucic acid is formed. Mucic acid is sparingly soluble in water, and has a characteristic crystalline form that often is used for the identification of galactose in an unknown mixture. Mucic acid differs from saccharic acid, formed by the oxidation of glucose, in the configuration on carbon atom four.



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

Galactose



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{COOH} \end{array}$$

Mucic Acid

Galactose on reduction gives the hexahydric alcohol, dulcitol, which is of little industrial importance.

Fructose.—D-Fructose, or fruit sugar, is found free in many fruits along with glucose. About half the sugar in honey is fructose. (Most of the remainder is glucose.) It is the sweetest sugar known. In the combined form D-fructose is widely distributed, since it comprises one-half of the molecule of ordinary table sugar, sucrose. The polysaccharide inulin is composed of fructose units. Inulin is the reserve storage carbohydrate that occurs in the roots of dahlia, Jerusalem artichokes, and the ti plant of the Hawaiian Islands.

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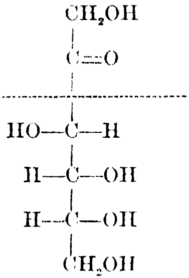
[*] *In vitro* ("in glass") means brought about in the test tube, in contrast with *in vivo* ("in the living"), meaning brought about in the living organism.

D-Fructose is levorotatory, its specific rotation being -93°. For this reason, fructose often is known as levulose.

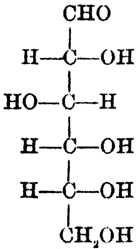
Fructose is a ketonic, rather than an aldehydic, sugar. This is demonstrated by the fact that on oxidation it does not yield an acid with the same number of carbon atoms as the starting material, but rather breaks at the point of the ketone group to form acids of lower carbon content.



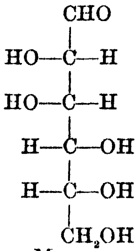
(Breaks here on oxidation)

D-Fructose

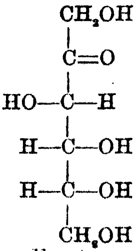
Interconversion of Fructose, Glucose, and Mannose.—If we consider the formulas of D-fructose, D-glucose, and D-mannose, we can see that the only difference in structure of the three is in the configurations around the first two carbon atoms. This is an important factor in a transformation that occurs in the presence of dilute alkali. If any one of the three sugars is allowed to stand in the presence of very dilute alkali, such as 0.05 N calcium hydroxide, it can be shown by qualitative tests that the solution contains a mixture of all three sugars. This is known as the



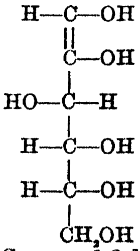
D-Glucose



D-Mannose



D-Fructose



Common 1-2 dienol

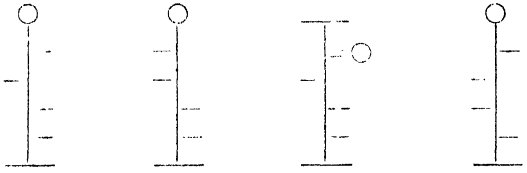
Lobry de Bruyn transformation. The explanation offered is that the interconversion takes place through an intermediate enol form common to all three. The term *enolization* sometimes is used to describe the change.

Enolization is not only of theoretical interest; it is a possible mechanism for the interconversion of these sugars in the living organism. Fructose reduces Fehling's solution, as do the aldohexoses, possibly because of the ease of conversion to one of the aldehyde forms in Fehling's solution, which is alkaline.

Osazone formation takes place more rapidly with fructose than with the aldohexoses. Fructose forms the same osazone as do D-mannose and D-glucose.

D-Fructose, the naturally occurring form, is fermented by yeast, but the L-form is not.

"Semaphore diagrams" are used sometimes as a convenient shorthand method of writing sugar formulas. A straight vertical line is used to indicate the carbon chain, a circle at the top to represent an aldehyde group, and a long horizontal line to represent a primary alcohol group. The positions of the hydroxyl groups are shown by short horizontal lines on one side or the other of the line representing the carbon chain. The formulas of the simple sugars, using the semaphore diagrams, can be written as:



D-Glucose D-Mannose D-Fructose D-Galactose

Disaccharides

The disaccharides can be considered as formed by the union of two monosaccharides with the loss of one molecule of water. All of them, therefore, have the molecular formula $C_{12}H_{22}O_{11}$. There are two large classes of disaccharides: the *reducing* sugars, which include maltose or malt sugar, lactose or milk sugar, and cellobiose; and the *nonreducing* sugars, which include sucrose, trehalose, and others.

Reducing Disaccharides.—Maltose. Maltose, or malt sugar, does not occur in the free state in nature. However, in the combined form it is widely distributed in the form of starch in the higher plants, and as glycogen in the animal body. Maltose is produced from barley by the malting process. Essentially, this process consists of the sprouting of barley under controlled conditions. The enzyme diastase formed during the sprouting, hydrolyzes some of the starch in the barley to maltose. This germinated barley is known as green malt. Dry malt is obtained by carefully drying the green malt at a low temperature so as not to destroy the enzyme. Dry malt is the form that is used in making beer and other malted beverages. If either green or dry malt is extracted with water and the solution is evaporated, the syrup obtained consists chiefly of maltose. This explains why the sugar frequently is called malt sugar.

In the human body starch is hydrolyzed by enzymes in the saliva and pancreatic juice to maltose (see pages 604 and 605).

Structure of Maltose.—Before we can write the structural formula of a disaccharide, it is necessary to have four items of information:

1. The monosaccharides yielded on hydrolysis.
2. The configuration, α or β, of the group taking part in the disaccharide union.
3. The carbon atoms involved in the union between the monosaccharides.
4. The kind of lactone ring present in the individual monosaccharides.

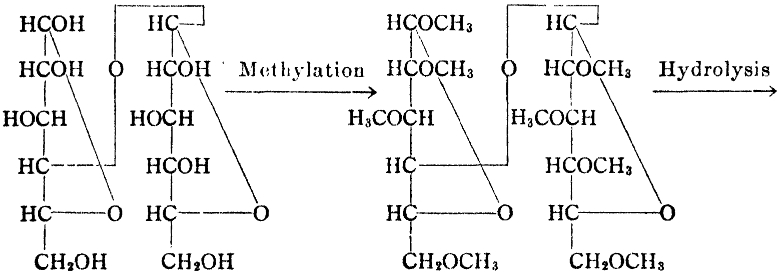
We shall now consider the evidence for the accepted structure of maltose.

1. There are two general methods of hydrolyzing compound sugars: first, by enzymes; and second, by acids. Maltose is hydrolyzed by the enzyme maltase to give two molecules of D-glucose. Dilute acids also hydrolyze it to two molecules of D-glucose.

2. It has been established by a number of investigations that maltase hydrolyzes α-glucoside linkages but does not split β-linkages; therefore, maltose must contain an α-glucoside linkage, since it is hydrolyzed by maltase. Maltase hydrolyzes not only the α-linkage in maltose, but also the α-glucoside linkage in any sugar.

3. and 4. The methylation studies of Haworth demonstrated which carbon atoms are involved in the linkage between the two glucose molecules, and also the kind of lactone rings present in each of the glucose molecules in maltose. In order to simplify the explanation of Haworth's work, we shall anticipate the formula for maltose, and then show the steps in the methylation studies that definitely establish the formula for maltose.

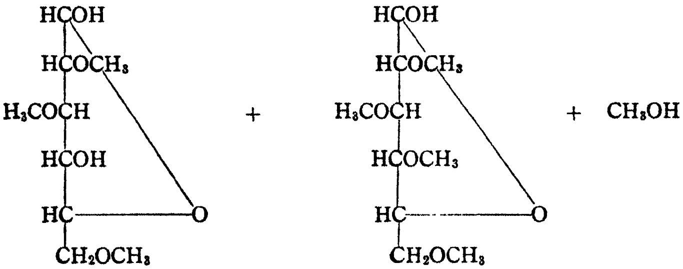
I II III IV



α-Maltose

Completely methylated α-maltose

V VI



2, 3, 6-Trimethyl glucose

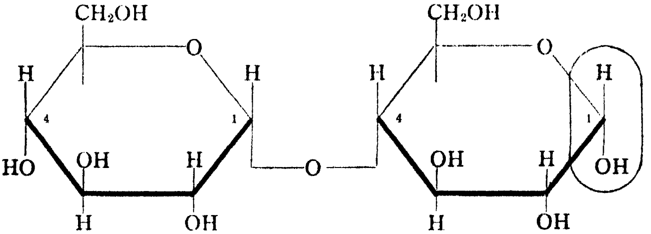
2, 3, 4, 6-Tetramethyl glucose

Methyl alcohol

If all the free hydroxyl groups in maltose are completely methylated by treatment with methyl sulfate and aqueous alkali, a methyl maltose derivative is obtained. When this derivative is hydrolyzed by acid to its constituent sugars, 2,3,6-trimethyl glucose and 2,3,4,6-tetramethyl glucose are obtained.

There is no methoxy ($-OCH_3$) group on number one carbon of V, because the acetal type of linkage on carbon number one in III easily splits off during the acid hydrolysis. The other methoxy groups in III and IV are ethers that are relatively stable to acid hydrolysis.

By means of a series of reactions too complicated to include here, the mixture of V and VI, the two methylated glucoses, can be separated into its components, which can be identified. The results show that the number four carbon atom of V must have been involved in some sort of union, since there is no free hydroxyl on this carbon atom available for methylation. We know that in all disaccharides one of the reducing groups is lost in the union between the two monosaccharides; therefore, carbon atom number one of one of the glucose units is involved in a linkage. Previous studies on glucose had demonstrated that the most common form of oxide ring was the delta lactone. Since there is no methoxy group on number five carbon atom in V and VI, it is logical to conclude that the oxide rings in the two units of maltose are delta lactones. The linkage between the two monosaccharides, therefore, must be a one-four-carbon atom linkage. The results show that formula I is the true structure of maltose. The perspective formula of maltose is:



α-Maltose
(α-glucoside α-glucose)

From the two ways of writing the structural formulas of maltose, it becomes evident why the perspective formulas are preferred to the straight-chain formulas. Valences cannot be thought of as bending sharp corners and extending through molecules.

The potential aldehyde group in one of the glucose units in maltose is free (circled in the above formula). The reducing properties of maltose are dependent on this fact. Maltose exhibits the reactions characteristic of all typical reducing disaccharides:

1. It forms an osazone. Maltosazone is soluble in hot water, but separates out on cooling.

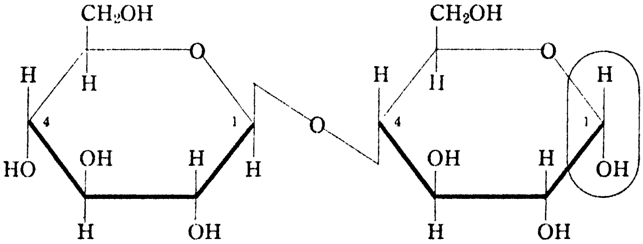
2. It reduces Fehling's solution.

3. It exhibits mutarotation. It is difficult for the beginner to visualize the point at which this rotation takes place in the disaccharides when the perspective formula is used. As is easily seen in the straight-chain formulas, the mutarotation takes place on carbon number one in the glucose unit that carries the potentially free aldehyde group. Obviously, the rotation takes place at the same spot in the perspective formula, although the reason that this is the only spot at which mutarotation can take place may not be so evident at first glance. The question often is asked by the uninitiated why mutarotation does not take place at the "other end" of the two hexagons. The carbon in question is the number four carbon atom, and mutarotation can take place only on a terminal carbon atom. In the perspective formulas a circle sometimes is drawn around the group capable of mutarotation.

The disaccharides really are glucosides, as is methyl glucoside (see page 331), the difference being that a sugar molecule has replaced the nonsugar group in other types of glucoside (e.g., methyl glucoside). In the system used for designating which monosaccharide has lost its reducing group in the disaccharide union, an *ide* ending is used. For example, α-D-glucoside signifies that the carbonyl of this glucose molecule is involved in the disaccharide union.

Maltose is the sweetening agent in various malt syrups. The sugar sometimes is used also in infant foods.

Cellobiose.—Another reducing disaccharide is cellobiose. It is well named since it is obtained from cellulose and contains two sugar units. If a pure form of cellulose, such as filter paper, is acetylated and carefully hydrolyzed, an acetyl derivative of cellobiose is obtained. When cellobiose is split by dilute acid, only glucose is obtained. The carbohydrate is not hydrolyzed by maltase, which shows that it does not contain an α-linkage. It is hydrolyzed by emulsin, and thus has a β-glucoside linkage between the two molecules. Methylation studies have shown that numbers one and four carbon atoms of the two glucose molecules are involved in the glucoside linkage. Also, the sugars have been shown to have a pyranose structure.

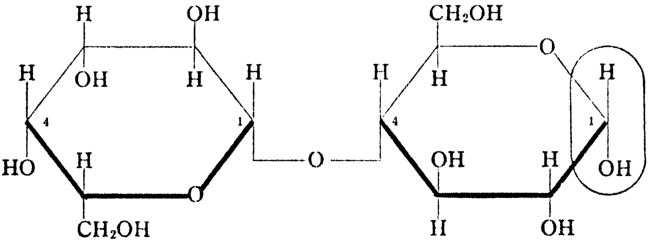


α-Cellobiose
(β-glucoside α-glucose)

The slight difference in the linkages of cellobiose and maltose strikingly illustrate the importance of small details of structure. Maltose is the principal constituent of starch, and cellobiose makes up the main part of cellulose. The only difference between the two disaccharides is that one has an α-glucoside linkage, while the other contains a β-glucoside linkage. We might say, therefore, that the slight difference between the α- and the β-glucoside linkages accounts for much of the difference in the digestibility of bread and wood.

Lactose.—Lactose is the disaccharide that occurs in cow's milk to the extent of about 4 per cent. It is the only carbohydrate found in the milk of all animals. Lactose forms an osazone that is soluble in hot water and separates on cooling. Since it is a reducing sugar, it exhibits mutarotation and reduces Fehling's solution. On hydrolysis, either by acid or by the enzyme lactase, lactose yields D-glucose and D-galactose. It is not hydrolyzed by maltase; hence it does not contain an α-glucoside linkage. It is hydrolyzed by emulsin; accordingly, it is known to contain a β-linkage. When lactose is oxidized with a mild oxidizing agent, it gives lactobionic acid, an acid containing a carboxyl group in place of the potentially free aldehyde group in the molecule. When lactobionic acid, in turn, is hydrolyzed by a mineral acid, gluconic acid and galactose are obtained. Hence the conclusion follows that the reducing group of glucose must be free in lactose (i.e., not tied up in the disaccharide linkage), since gluconic acid is the oxidation product of glucose. Lactose is known, therefore, to be a glucose-galactoside sugar.

The methylation studies of Haworth definitely established that the number four carbon atom of glucose is involved in the disaccharide union. These studies also established the presence of delta lactone rings in the monosaccharides of lactose. With this information the structural formula for lactose can be written:



α-Lactose
(β-galactoside α-glucose)

α-Lactose is the usual form encountered, but if the disaccharide is crystallized above 95° C., the β- form is obtained. This transformation is important because β-lactose is more soluble and has a sweeter taste than the α-form. Lactose is only about one-sixth as sweet as cane sugar, and is less soluble in water than the other sugars. β-Lactose is used in infant food when it is necessary to get as much lactose as possible into solution and to have the mixture palatable. β-Lactose is obtained by spraying α-lactose into heated, rapidly revolving drums.

Lactose is fermented only slightly or not at all by ordinary yeasts. Certain bacteria, however, convert it to lactic acid. As was mentioned previously, lactic acid is produced commercially from the lactose in whey.

Nonreducing Disaccharides.—Sucrose. Sucrose is the most common and, commercially, the most important disaccharide. It is the substance usually referred to as "sugar." Sucrose is widely distributed in plants, and is found in varying amounts in practically all plant cells. In the stalk of sugar cane it constitutes from 12 to 20 per cent of the green weight. About 15 to 20 per cent of the fresh weight of sugar beets also is sucrose. Sugar cane and sugar beets are the two commercial sources of this disaccharide. Sucrose also is present in considerable quantities in the sap of sugar maple and in the stalks of sorghum cane. These, however, are not used as sources of the crystalline product.

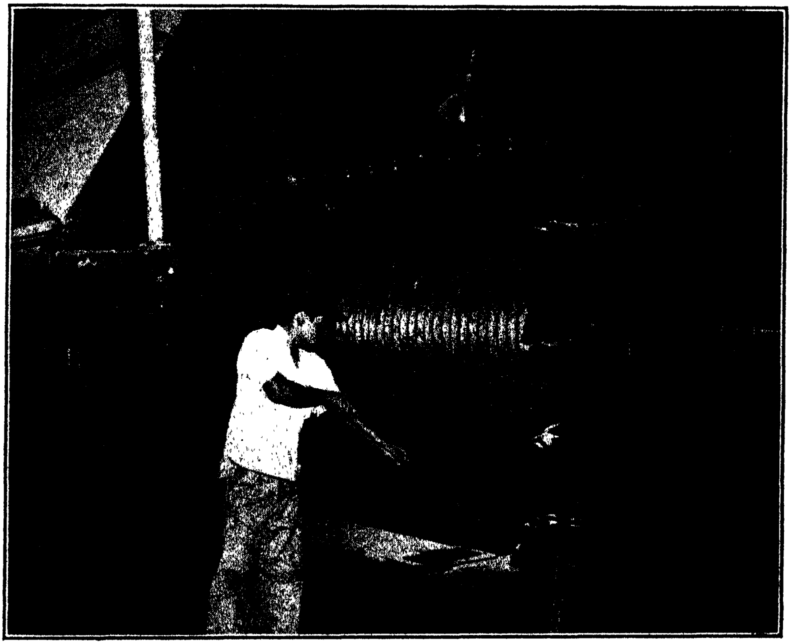
Fig. 45.—Sugar cane seedlings being fed into the hoppers of a tractor-driven machine that furrows, plants, fertilizes, and covers the seedlings at the rate of 12 acres a day on one of the scientific farms in the Territory of Hawaii. (Courtesy of the Pan-Pacific Press Bureau Photo.)

Sugar has an interesting history. There are references to it in the Chinese literature of 700 B.C. The soldiers of Alexander the Great, returning from India, told stories of "wool without sheep and honey without bees." We know now that they were referring to cotton and sugar cane. The Arabs knew of the culture of sugar cane. As the Moslem sickle moved south and westward, it carried the knowledge of sugar cane culture with it. The Arabs brought to Europe a kind of edible gravel that they called "sukkar." They brought to Spain such advances in civilization as arithmetic, algebra, soap, and sugar cane. The Spanish conquistadors introduced sugar cane to the unwilling natives of the West Indies, where it has flourished ever since.

Fig. 46.—Cane field in Hawaii. This is a typical field of sugar cane in the United States Territory of Hawaii, which normally produces about one-sixth of the nation's domestic supply. (Courtesy of the Pan-Pacific Press Bureau Photo.)

The most intensive cultivation of sugar cane, and probably the most profitable, is carried out in the Territory of Hawaii where there are about 250,000 acres of sugar plantations. On these plantations, much of the planting is done by machinery to eliminate hand labor. As Fig. 45 shows, cuttings rather than seeds are used for planting. More chemical fertilizer is used for Hawaiian sugar cane than for any other staple crop in the world. The annual bill for such material ranges between 4 and 7 million dollars. Each pound of sugar in growing requires approximately 4,000 pounds of water.

The cane is mature in from twelve to twenty months. At that time the stalks are from 10 to 30 feet long and from 1 inch to 2½ inches in diameter. When a field is ready for harvesting, it is "fired." As the cane grows, the lower leaves fall off, and at maturity they form a matted mass at the base of the stalks. If these were not removed, they would impede harvesting, and if permitted to reach the mill, they would lower the mill's efficiency. The fields usually are burned when they are dry and when there is a fairly strong wind so that the fire will quickly sweep across the field without materially damaging the stalks. The stalks are then cut into convenient



A.

Fig. 47.—*A*, In the sugar mill the cane is sent through giant steel rollers, like that shown in the illustration, by which the juice is extracted. It then is boiled, evaporated, and made into "raw" sugar. *B*, Raw sugar sacked and stored, awaiting transportation by ship to the United States, where final processing is completed. (Courtesy of Pan-Pacific Press Bureau Photo.)

lengths by workers with heavy knives called machetes. The cane is transported to the mills by portable railways laid in the field, or by motor truck, or from a few plantations by flumes, such as are used in the Pacific Northwest for moving logs down steep grades.

The cane on entering the mill passes through a series of corrugated crushing rollers and then through smooth rollers which press out the juice. The juice is pumped into huge tanks. Milk of lime is added to stop fermentation, to neutralize organic acids, and to precipitate impurities. Heating coagulates any protein present, and this protein then is removed as a scum. After a period of standing during which heavy impurities settle out, the clear juice is run into evaporators, where it is concentrated under reduced pressure to a thick syrup. This syrup is concentrated further in vacuum pans, and actual crystallization begins. The viscous, sticky mass from the vacuum pans, known as *massecuite,* then is run into a basket centri-

B.

fuge lined with very fine brass screens. The screens retain the sugar but allow the molasses to escape to an outer casing. The hard, pale brown mass that remains in the centrifuge constitutes the raw sugar that is sacked and shipped to the mainland for further purification. This raw sugar is from 88 to 97 per cent

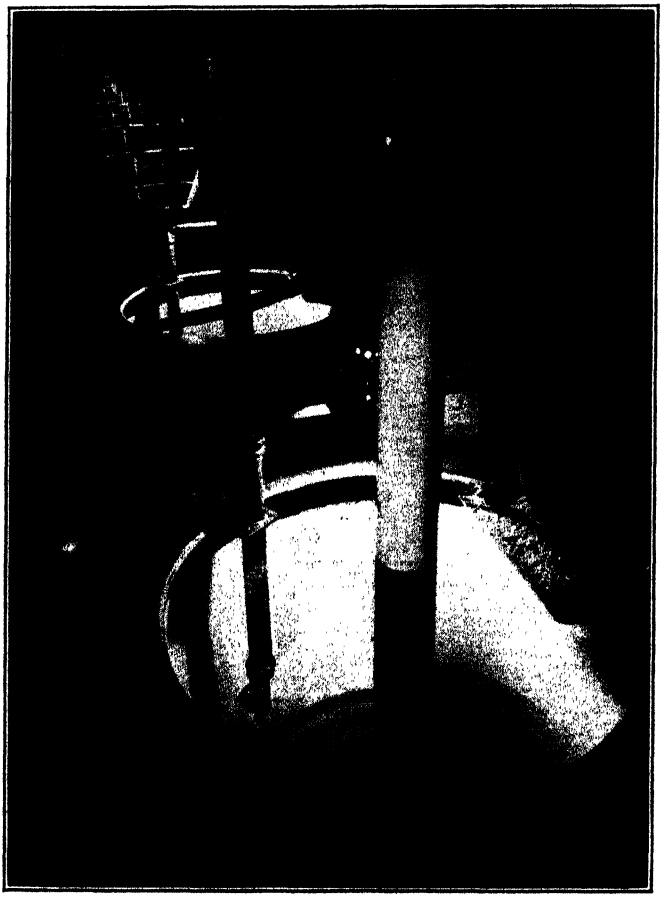


Fig. 48.—Centrifuges used in the final purification of cane sugar. (The same type of equipment can be used for purifying beet sugar.) Massecuite, a mixture of sugar and molasses, is poured into the centrifuge basket, the inside of which is lined with a fine-meshed brass screen. As the centrifuge revolves at a high speed, the screen retains the sugar, but allows the liquor or molasses to escape to the outer casing. (Courtesy of C & H Sugar Refining Corporation.)

sucrose. On the mainland the sugar is refined and decolorized to give a product of 99+ per cent purity.

The only rival of "king cane" is the sugar beet. The development of beets as a source of sugar took place during the Napoleonic Wars. France's supply of sugar from the West Indies was cut off by the English blockade, and Napoleon offered a prize of a million francs for a practical process of obtaining sugar from beets. By plant breeding and selection the percentage of sugar in beets was raised from 6 to 18 per cent. By 1913 beet sugar production equaled that of cane sugar.

The sugar in beets is exactly the same chemical compound as that in sugar cane, and if the commercial products are of the same degree of purity, there is no difference between them. Formerly, it was more difficult to remove the impurities from beet sugar, and hence a prejudice arose in favor of cane sugar for candy and jelly making, but this prejudice has largely disappeared, with improved methods of refining beet sugar.

The specific rotation of sucrose is +66.5°. This physical property is important since it is utilized in the quantitative determination of sucrose. A special type of polarimeter, known as a saccharimeter, has been developed. In this instrument the scale is so arranged that it indicates directly the per cent of sucrose in the solution. Enormous quantities of crude sugar are imported, and since there is an import duty, the saccharimeter is used as a quick and convenient method for determining the amount of sucrose present.

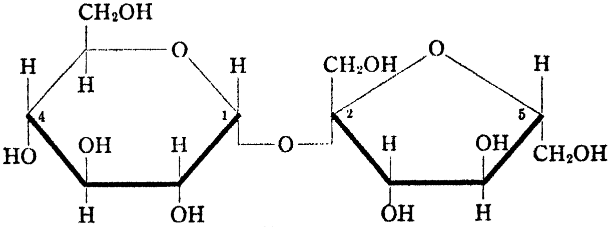
Sucrose is distinguished from the other disaccharides by being more stable to alkali and more sensitive to acid. It is 1,000 times easier to hydrolyze than maltose or lactose. Even weak acids, such as citric or tartaric acids, hydrolyze it to the monosaccharides, D-glucose and D-fructose. Sucrose also can be hydrolyzed by the enzyme *invertase,* present in yeast, to give an equal molecular mixture of glucose and fructose. This mixture is known as *invert sugar.*

Invert sugar differs in three particulars from the original solution of sucrose. In the first place, it contains twice as many molecules, which means that the solution will have a lower vapor pressure, as reflected in its increased tendency to take up water.

Secondly, it is sweeter than the original sugar. If sucrose is given an arbitrary "sweetness" value of 100, invert sugar on this basis has a value of 130. These two properties are utilized in the making of cream fillings, such as fondant, for chocolates. A small amount of invertase is incorporated in the filling, and as the candy ages, the sugar hydrolyzes and the filling continually becomes sweeter and softer.

A third respect in which invert sugar differs from sucrose is in its specific rotation. The specific rotation of invert sugar is –20.5°, while that of sucrose is +66.5°. Such a wide variation is explained by the fact that the glucose liberated in the hydrolysis has a specific rotation of +52.5°, while that of the fructose set free is –93°. The –20.5° represents an equilibrium between the glucose and fructose forms. The inversion (change of sign) of rotation that occurs when sucrose is hydrolyzed explains the origin of the term *invert sugar.*

Sucrose shows none of the properties of a reducing sugar: 1. It does not form an osazone. 2. It does not reduce Fehling's solution. 3. It does not react with hydrocyanic acid. 4. It does not exhibit mutarotation. Therefore, the reducing groups of both glucose and fructose must be tied up in the disaccharide linkage. Paradoxically, although sucrose was the first sugar known, and is the most abundant, it chemical structure was the last to be established. When fructose is combined in sucrose, it contains a gamma-lactone ring. As soon as sucrose is hydrolyzed and free fructose is obtained, the gamma-oxide ring rearranges to a delta-lactone form. Sugars that contain a gamma-lactone ring are very reactive; this explains the difficulties encountered in establishing the structure of sucrose. The following is the proposed structure of sucrose:



Sucrose
(α-glucoside β-fructoside)

No free reducing group is present in sucrose, and mutarotation is impossible. Hence, there are no α- and β- forms of sucrose. This is said to be the reason that sucrose crystallizes more easily than do the reducing disaccharides.

The first unquestioned synthesis of sucrose was carried out in 1944 by Doudoroff et al. They demonstrated that in the presence of a purified enzyme, *phosphorylase,* fructose and glucose-1-phosphate react to give inorganic phosphate and sucrose.

Trehalose.—Trehalose is widely distributed in fungi; it also is found in bacteria and yeasts. Apparently it replaces sucrose in the forms of plant life that do not contain chlorophyll. Trehalose is α-glucoside α-glucoside, and hence it does not contain a reducing group.

Trisaccharides

All the trisaccharides have the molecular formula $C_{18}H_{32}O_{16}$. The best known sugar of the group is raffinose. It occurs in appreciable quantities in sugar beets; in fact, enough is present so that a correction must be applied to a saccharimeter reading for beet sugar. It is found in a higher concentration (nearly 8 per cent) in cottonseed meal than in any other known product. Raffinose is not isolated as such, but this proportion in all the cottonseed cake produced each year would amount to nearly 100,000 tons of the sugar. Raffinose is a nonreducing sugar. On hydrolysis with mineral acids it gives equal proportions of fructose, glucose, and galactose.

Study Questions

1. What are the subgroups into which the monosaccharides can be divided?
2. List three items of evidence that support the conclusion that D-glucose exists mainly in a pyranose structure in aqueous solution.
3. Write an equation for a reaction that shows that D-glucose has an aldehyde group at one end of the carbon chain.
4. Give at least two reasons why osazones are used for identification purposes.
5. Define mutarotation. How does a closed-ring formula for each form of glucose help to explain mutarotation?

6. Name and give the occurrence of each of the naturally occurring hexoses.
7. Write the graphic formula and supply the proper name for the two closed-ring forms of D-glucose that exist in an aqueous solution at equilibrium.
8. Name the three naturally occurring pentoses and give the occurrence or importance of each.
9. What is the disaccharide obtained by cautious hydrolysis of cellulose? What monosaccharide units does it give on hydrolysis?
10. What is the nonreducing disaccharide found in sugar cane?
11. In what two particulars does invert sugar differ from a solution of the disaccharide from which it is derived?
12. Write the equation for the reaction of 12 per cent hydrochloric acid on pentoses, naming all compounds involved. What is the function of pentoses or pentosans in certain plants?
13. What three facts must be known in order to determine the structural formula of a disaccharide?
14. What monosaccharides are obtained on hydrolysis of raffinose?
15. What is the disaccharide found in milk and what sugars are obtained on hydrolysis? How is the β-modification of this sugar obtained and what are its advantages over the α-form?
16. What is the formula for malt sugar?
17. Define carbohydrates.
18. Why is ribose an important pentose?
19. Essentially, what is the structural difference between starch and cellulose? Use diagrams to illustrate your answer.
20. Show by a series of equation the steps in the formation of glucosazone.
21. If glucose exists mainly in the closed-ring structure, why does it ever give aldehydic reactions?
22. Show the steps in the cyanohydrin synthesis of D-glucose from D-arabinose.
23. What is the name of the simplest possible sugar? Write the formula for this compound.
24. What is the significance of the D- or L- designation before the name of a sugar?
25. Why is Benedict's solution more frequently used than Fehling's solution in testing for the presence of glucose in urine?
26. What is the name of the monocarboxylic acid of glucose? If this acid is subjected to further oxidation with dilute nitric acid, what product results?
27. What are several names for the closed-ring structure in glucose and many of the other sugars?
28. What advantages do perspective formulas possess over the straight-chain type of formulas?

29. What is an industrial use of D-mannitol? How is it obtained for this purpose?
30. What is a natural food that is rich in fructose?
31. How does the *Lobry de Bruyn transformation* explain the interconversion of fructose, glucose, and mannose? What is the term employed to describe this change?
32. Describe briefly the manufacture of sugar from cane.

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CHAPTER XV

POLYSACCHARIDES AND RELATED COMPOUNDS

Introduction.—The polysaccharides, in contrast to the sugars, do not have a sweet taste, and have little or no reducing properties. They are substances of high-molecular weight, formed by the union of a number of monosaccharide molecules with the elimination of water. Most of the substances of this group of carbohydrates are insoluble in water, and, when they are brought into solution by physical or chemical reagents, they form colloidal, rather than true, solutions in water. Because of their high-molecular weight and their complex structure, the chemical composition of these compounds as yet is not clearly defined in all cases. The relation of the polysaccharides to the other groups of carbohydrates already has been represented in the diagram on page 315. The polysaccharides can be subdivided further into the following groups:

- Pentosans $(C_5H_8O_4)_n$
  - Arabans
  - Xylans
- Hexosans $(C_6H_{10}O_5)_n$
  - Reserve polysaccharides
    - Starch
    - Glycogen
    - Inulin
  - Structural polysaccharides
    - Cellulose
    - Hemicellulose
  - Mixed or acidic polysaccharides
    - Pectins
    - Gums
    - Mucilages

Pentosans

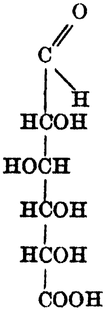
The pentosans, as the name indicates, are substances composed of a large number of pentose molecules. The pentosans as a class have not been investigated as thoroughly as have the hexosans. They comprise about 25 per cent of the weight of wheat, oat straw, and of the dry weight of wheat brans. The pentosan *xylan* has been isolated from such sources as corn cobs, cereal straw, and cottonseed hulls. On hydrolysis it yields *xylose.*

The pentosans that yield *arabinose* on hydrolysis are known as *arabans.* They occur most abundantly in gum arabic, cherry gum, and mesquite gum. The arabans also are found associated with pectin. The pentosans are highly hygroscopic, and function in plants, especially in cacti, as water-retaining substances.

When pentosans are heated with mineral acids they yield furfural (see page 318). Furfural rapidly is becoming an important industrial chemical.

The question as to whether the pentoses are primary products of photosynthesis or whether they are formed from hexoses will now be considered. The evidence at the present time favors the theory that hexoses are the primary products of photosynthesis and that the pentoses are secondary products formed by loss of carbon dioxide from the hexose uronic acids. In order to understand this mechanism, it will be necessary to consider the structure of the uronic acids.

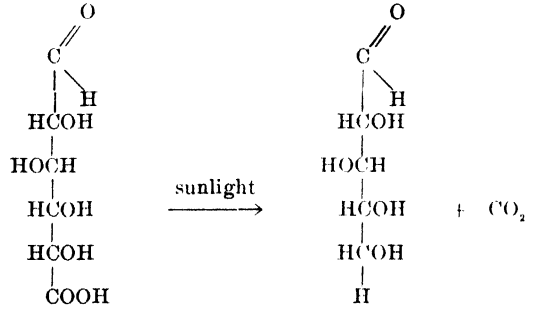
In the aldose sugars the most reactive part of the molecule is the aldehyde group; therefore, chemical reactions of these sugars involve this group. The aldehyde group in disaccharides or other glycosides is combined and thus removed from the sphere of chemical reactivity. A mild oxidizing agent acting on such a glucoside would, therefore, attack the primary alcohol group



D-Glucuronic acid

at the opposite end of the chain and convert it to a COOH group. If the aldehyde group is now set free by the hydrolysis of the glucoside, glucuronic acid is formed.

Spoehr found D-glucuronic acid to be present in cacti, which also contain large quantities of pentosans. On the basis of these observations, the theory was advanced that pentoses were formed by the loss of carbon dioxide from hexose uronic acids. The theory is strengthened by the fact that a solution of D-glucuronic acid loses carbon dioxide when exposed to sunlight. Additional support was given the proposed mechanism by the observation that D-glucose and D-xylose usually are associated in nature. The formation of D-xylose by the loss of carbon dioxide from D-glucuronic acid is illustrated by the following equation:



Hexosans

Starch.—The principal storage carbohydrate of plants is starch. It is found most abundantly in the parts of the plant used for propagation; for example, in the seeds of cereal grains; in tubers, such as white potatoes; and in roots, such as the sweet potato. It functions as a reserve food supply for the embryo until leaves and roots are formed. Starch, however, is not the universal reserve material in plants, because such oil-bearing seeds as soybean are almost free of it.

Sources of Starch.—In the United States most of the starch for commercial purposes is obtained from corn. In Europe the principal source of starch is the white potato. Other sources of starch that are of commercial importance are wheat, rice, the sago palm, and a tropical American plant, *Maranta arundinacea,* from which arrowroot starch is obtained. The production of starch from sweet potatoes became of commercial importance in 1941. Of the noncereal starches, tapioca, or cassava, has been the most important in the United States. The amount imported in a normal year such as 1939 was 382 million pounds. This kind of starch is obtained from the tuberous roots of the plant *Manihot utilissima,* which is grown principally in the East Indies.

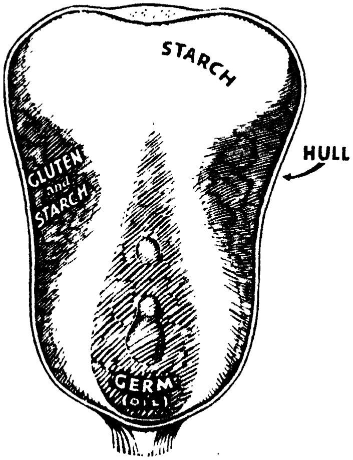


Fig. 49.—Diagram showing the structure of the corn kernel. Starch is the principal component, the kernel containing about 60 per cent of this substance. In the starch manufacturing industry the gluten and the hulls are made into feed for livestock. The germ contains a high percentage of oil, which, after purification, is used for salad oils and vegetable shortenings. (Courtesy of the Corn Industries Research Foundation.)

Methods of Isolation.—In the manufacture of starch from corn, the clean corn kernels are steeped in huge tanks for two days with warm water containing about 0.25 per cent sulfur dioxide. The steeping loosens the hull and softens the gluten. The sulfur dioxide functions to prevent fermentation during the soaking. After the steeping process, the corn is put through "degerminating" mills, which tear the kernel apart but do not crush the germ. The crushed material from these mills is washed into tanks called germ separators. The germ, because of its oil content, is lighter than the remainder of the kernel, and thus floats to the stop and is skimmed off. The remainder of the kernel is then wet-ground between mill stones in order to separate the starch and gluten from the fragments of fiber and hull. The wet mass from these mills is washed onto a series of reels and shakers covered with bolting silk.

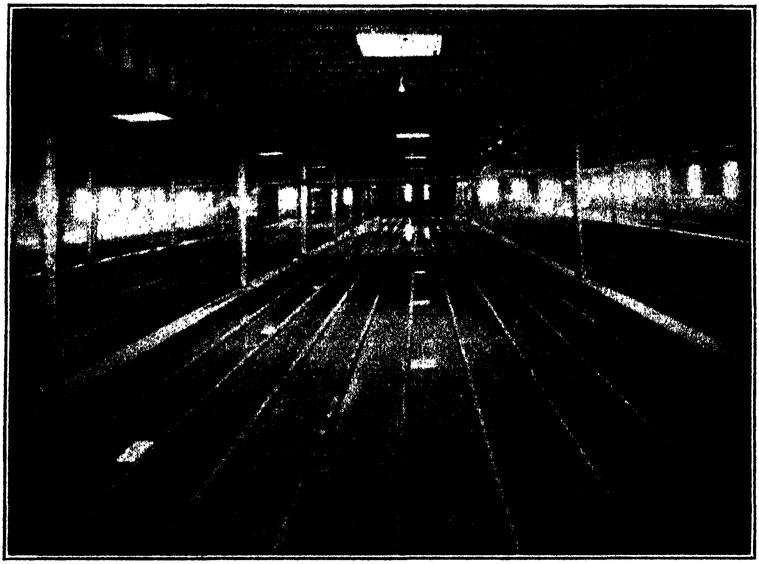


Fig. 50.—Starch tables. These flat-bottomed troughs or tables are about 120 feet long, 2 feet wide, and have vertical sides 8 to 10 inches high. A water suspension of starch and gluten from the milling process is run onto the tables, which are slightly inclined so that the mixture will flow slowly along them. The starch, being heavier, settles out while the lighter gluten and soluble material are discharged at the end of the trough. After a layer of starch several inches thick has settled out, the flow of the starch suspension is stopped, and the starch is removed from the table by flushing with water. (Courtesy of the Corn Industries Research Foundation.)

The gluten and starch pass through the bolting silk, but the fiber and hulls are retained. The suspension of starch and gluten, known as starch milk, is then run onto the starch tables illustrated in Fig. 50. Starch, having a specific gravity of 1.5 to 1.6, is heavier than the gluten, and settles out as the suspension flows along the gently sloping trough. If dry starch products are to be made, the starch, after retabling, is ready to be kiln-dried and placed on the market. The wet starch can be used for conversion to corn syrup or dextrose.

A common method of separating potato starch is to allow the starch suspension to stand in large settling tanks for ten to twelve hours. Most of the protein and other material remain suspended and can be drawn off while the starch settles out as a compact layer.

Centrifugation frequently is employed as a method of separating and purifying starch after it has been washed from the starch-containing material.

Importance of Starch.—One reason that starch has been studied extensively is that it has been known for a long time to be a plant component. Its detection in plants is easy due to the characteristic blue color it yields with iodine. Another reason is that it is relatively easy to separate and purify for research studies. Another incentive for investigations on starch has been the knowledge that it is one of the most important energy foods for man and the higher animals. Furthermore, starch is an important raw material for many industries. There are few substances that have more technical or domestic uses than starch and its modified forms.

Physical Properties of Starch.—Starch occurs in the plant in the form of microscopic granules. The size, shape, and markings, or striations, on these granules are characteristic of the particular species. The general shape and form of the starch granules of a particular species is so constant that the source of a sample of starch often can be determined by a microscopic examination. The morphological characteristics of starch granules even have been used for the classification of plants.

Potato starch granules are among the largest, some being as large as 100 microns in diameter. Corn and wheat granules are intermediate in size. There is a wide range in sizes, from very small to large, among the granules of wheat starch. Cornstarch granules vary in size from about 10 to 25 microns in diameter. They tend to be hexagonal in shape, probably because the pressure under which they are formed forces them into a honeycomb structure. Rice starch granules are among the smallest (3 to 8 microns in diameter).

Raw starch is insoluble in cold water, but if a suspension of starch and water is heated to a temperature of 60° to 70° C., depending on the kind of starch, the granules swell enormously to as much as 25 times their original volume. This phenomenon is known as heat gelatinization, and the temperature at which most of the granules swell is known as the gelatinization temperature. This gelatinized starch will set to a gel on cooling, provided the concentration of the starch is sufficiently large.

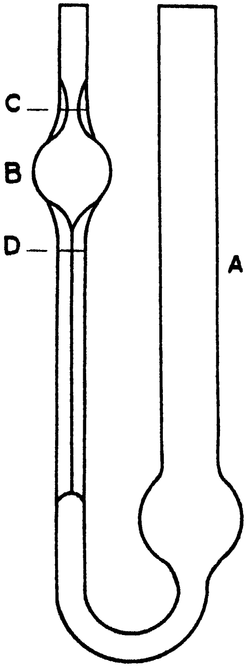


Fig. 51.—Ostwald viscosimeter. See text.

An observation of the process of heat gelatinization under the microscope reveals that at the gelatinization temperature, the starch granules appear as large, balloon-like vesicles filled with an opalescent, colloidal solution. If the solution is heated further, or is stirred or shaken, these granules burst.

The gelatinization of starch can be accomplished also by the action of chemical reagents, such as sodium hydroxide, potassium hydroxide, potassium thiocyanate, sodium salicylate, urea, and dilute hydrochloric acid or sulfuric acid. These are known as *cold* gelatinizing agents.

The property most widely used in characterizing starches is the viscosity of their gelatinized suspensions. Viscosity is a measure of the internal friction of a liquid. It results from the resistance to the passage of one layer of the liquid over another. In many gelatinized starch preparations this viscosity is due mainly to the jostling of the swollen granules. Most of the viscosity measurements on starch preparations have been carried out in the Ostwald capillary type of viscosimeter. Such measurements are used in the routine testing of samples of starch to determine their suitability for various industrial purposes, such as adhesives and textile sizings.

To make a viscosity determination, an accurately measured quantity of liquid is introduced through Tube A, Fig. 51. The liquid is allowed to stand in the viscosimeter until it reaches the temperature of the water bath in which the viscosimeter is immersed. Suction is applied on the small arm of the viscosimeter until the upper meniscus of the liquid reaches a point above C. The suction then is released, and when the meniscus passes point C, the time of flow between points C and D is measured accurately by means of a stop watch. For most purposes relative viscosity is all that is needed. The relative viscosity of a liquid, such as a starch suspension, is obtained by dividing the time of outflow for the liquid by the time of outflow for water.

Chemical Structure of Starch.—The first significant observation pertaining to the structure of starch was made in 1811 by Kirchoff, who obtained a sugar by boiling starch with dilute sulfuric acid. This sugar later was shown to be dextrose (D-glucose). Since then it has been shown repeatedly that hydrolysis of starch with acids yields D-glucose as the only monosaccharide. The disaccharide formed by the hydrolysis of starch with the enzyme diastase was isolated by Saussure in 1819, subsequently by Dubrunfaut in 1847, and "rediscovered" in 1872 by Sullivan, who named it maltose. A very voluminous literature on starch has accumulated through the years. In 1947 Schoch, an authority on the chemistry of starch, stated that the literature on this field contained more than 6,000 references. A large number of these have been concerned with the structure of starch. This will give the student an idea of the complexity of the subject.

Two universally accepted facts about starch are that (1) D-glucose is the only monosaccharide formed on acid hydrolysis and (2) maltose is the only disaccharide formed by enzymatic hydrolysis. Since maltose is the disaccharide unit of starch, it follows that the α-1,4-glucosidic bond present in maltose is the principal linkage of glucose units in starch. The evidence from methylation studies to prove that maltose is an α-1,4-glucoside has been given already in connection with the discussion of the structure of that disaccharide.

Methylation studies also were applied to starch by Haworth, Hirst, and co-workers. Hydrolysis of the methylated starch gave principally 2,3,6-trimethyl glucose, which is to be expected if starch is a polymer of glucopyranose units linked as in maltose. In addition, 4 to 5 per cent of tetramethyl glucose also was isolated. The presence of the tetramethyl glucose was explained as arising from glucose units at the ends of chains where hydroxyl groups on the number 2, 3, 4, and 6 carbon atoms would be free for methylation. On the basis of the relative amounts of trimethyl and tetramethyl glucose obtained, Haworth concluded that the starch molecule was made up of 25 to 30 glucose units. This concept was accepted for several years, but additional data began to point to a much larger molecular size. For example, the results of viscosity and osmotic pressure measurements indicated a molecule with many more than 30 glucose units. The reducing values of starch determined by new methods denoted a molecule containing several hundred glucose units.

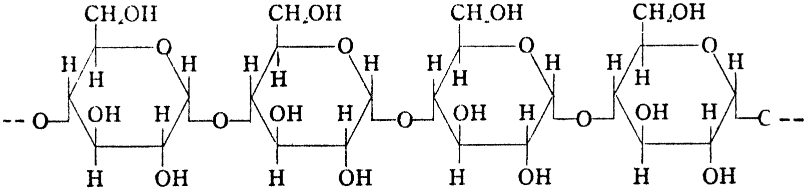
To explain these inconsistencies between the molecular weight estimated by end group assays and by other methods, Staudinger, among others, proposed a branched chain type of molecule for starch. This concept had to be modified, too, but it was very useful in pointing the way for more fruitful research.

Components of the Starch Granule.—That starch is composed of two components structurally different in their types of molecule is no longer seriously questioned. The question as to the existence and nature of these two components was argued in the chemical literature for a century without arriving at any conclusive answer. It is only within the past decade that real progress has been made in explaining the behavior of starch on the basis of its structure and composition.

One of the principal reasons for recent progress in the elucidation of the structure of starch was the development of methods of separating the starch components in a high state of purity without chemical degradation. Perhaps the most significant advance in this field was a discovery by Schoch. He found that if starch was suspended in water containing 12 per cent n-butanol and autoclaved for two hours, one component of the starch separated on cooling as microcrystals. The component that precipitates is called *amylose,* and the one that remains in solution is named *amylopectin.*

Since the original use of butyl alcohol for the precipitation of the amylose, or A-fraction, it has been found that selective precipitation of the amylose can be effected by many substances capable of acting as a donor or acceptor in hydrogen bonding. These polar compounds include many of the aliphatic monohydroxy alcohols and the nitroparaffins, such as 2-nitropropane. Hayworth and co-workers claim a better separation of the two components by the use of thymol and cyclohexanol.

The components of starch granules differ in their molecular structure and properties. It is now generally accepted that the amylose component has a linear or unbranched structure containing 100-700 glucose units.



Portion of the amylose chain

Other characteristic properties of amylose are:

a. It yields a pure, brilliant blue color with iodine. It has been suggested that a helical form of the linear amylose component is essential for the formation of the blue color. When treated with iodine it is thought that the iodine molecules are deposited within the spirals, the spaces of which are of the exact size to allow the iodine to enter.

b. Amylose solutions exhibit a low solution stability at ordinary concentrations. The reversion of solubilized starch to an insoluble form is termed *retrogradation*. It is thought to be due to lengthwise association of the linear amylose chains. The speed of retrogradation is dependent on the concentration of the starch solution. Thus a 1 per cent solution will remain clear for several days, while a 2 per cent solution will flocculate overnight. Once starch has retrograded, it is very difficult to redissolve.

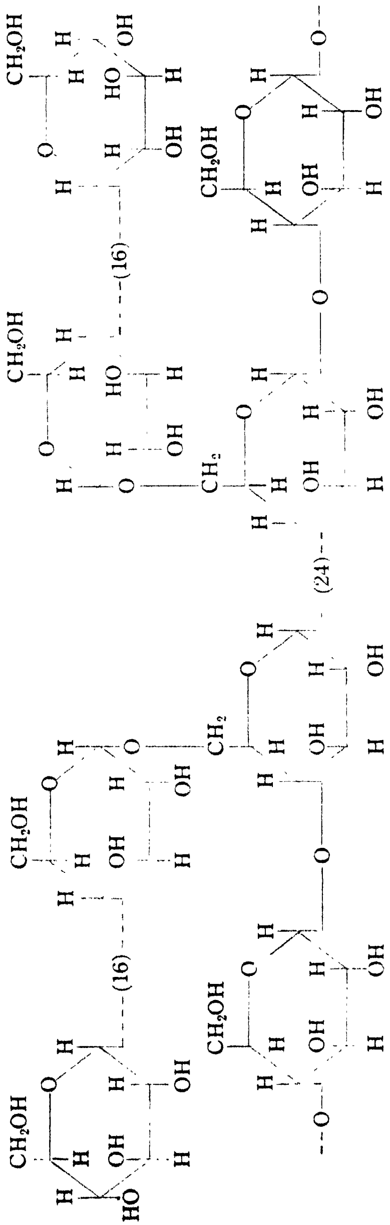
c. Amyloses are hydrolyzed to maltose to the extent of 99 per cent or more by the enzyme β-amylose.

d. The acetyl derivatives of amylose can be fabricated into films and fibers of high tensile strength. The ability to form strong fibers has been shown to be a property of long chain types of polymers.

Amylopectin, the other component of starch, consists of giant, branched or treelike molecules containing both α-1,4 and α-1,6 glucosidic linkages. The prevailing concept of the structure of the amylopectin molecule is represented by the formula on page 363.

Branching occurs on the average at about every 25th glucose unit through the 6th hydroxyl group of the glucose units. Thus, approximately every 25th glucose unit has, in addition to the adjacent unit attached at the 4th carbon atom, another attached at the 6th position. The outer branches are thought to consist of 18-20 glucose units. Authorities on the chemistry of starch agree that the molecular weight of amylopectin is large but its exact magnitude is uncertain. Reported values indicate amylopectin contains 500 to 5000 or more glucose units.

The characteristic properties of amylopectin are: (a) The color with iodine is red to purple. (b) Solutions of amylopectin in water, even in concentrations of 5 per cent, are stable; i.e., they do not retrograde on standing. (c) Amylopectin is incompletely hydrolyzed by the enzyme β-amylase, only 50 to 60 per



Portion of the Amylopectin Macromolecule cent being hydrolyzed to maltose. Cessation of enzyme action is thought to result from inability to hydrolyze 1,6-glucosidic linkages. (d) Acetylated amylopectin films are so weak and brittle that their tensile strength cannot be determined. The sharp contrasts between the properties of the two components of starch will be appreciated when those just listed are compared with the properties of amylose given previously.

It has been found that in most starches the amylose or linear form is the minor component of the starch granule. Tapioca and rice starches contain 17 per cent amylose; banana, corn, potato, and wheat starches contain between 21 and 24 per cent amylose.

Starch from waxy or glutinous corn and sorghum contains only amylopectin. Waxy corn starch was used during the war as a substitute for tapioca starch. At the other extreme, starch from wrinkled seeded garden peas has been shown to be about 70 per cent amylose. This is nearly twice the amylose content reported for any other starch. Strangely enough, starch from smooth seeded peas is essentially like the cereal starches in its amylose content.

For most of the common applications of starch, the amylopectin component is the one that is more useful. This is true where starch is employed as a thickening agent, as a protective colloid, or as sizing for paper and textiles. Recent work indicates that the aggregation of amylopectin and not amylose mainly is responsible for the staling of bread. It has been established that all starches are not composed entirely of carbohydrate. Raw cereal starches such as those from wheat and corn contain nitrogen, phosphorus, and as much as 1 per cent fatty material. These noncarbohydrate materials are held by secondary valence forces, since they are removed by exhaustive extraction with hot 85 per cent methanol or 80 per cent dioxane. On the other hand, extraction of potato starch does not materially reduce its phosphorus content. This has led to the conclusion that the phosphorus in this case is present as a phosphoric acid ester, probably of the hydroxyl group on the 6th carbon atom of glucose residues.

Polysaccharides that closely resemble amylose and amylopectin have been synthesized in the laboratory. Phosphorylase, an enzyme present in potato juice and muscle, acting on glucose-1-phosphate under the proper conditions forms a polysaccharide that gives a deep blue color with iodine, is completely hydrolyzed by β-amylase, and retrogrades rapidly from solution. In addition, analyses indicate that it is an unbranched chain containing from 50 to 200 glucose units. Hence it closely resembles the amylose component of natural starches. Dr. and Mrs. Cori of Washington University in St. Louis received a part of the 1947 Nobel prize for their isolation of crystalline muscle phosphorylase and their other research on the elucidation of the mechanism of glucose-glycogen transformations in the animal body.

Bourne and Peat in England have reported the preparation of a polysaccharide that resembles amylopectin in its properties. Purified potato phosphorylase and another enzyme from the same source (Q enzyme) acting on glucose-1-phosphate form a glucose polymer that stains red-purple with iodine, is easily soluble in water, and is only 60 per cent hydrolyzed by β-amylase. It is conceivable that the characteristic properties of various starches may be determined by the relative proportions of these two enzymes in plants. A striking fact is that enzymatic synthesis of starch components does not take place unless a trace of natural starch or glycogen is present as an enzyme activator or initiator. One of the most plausible hypotheses proposed is that a certain chain length of glucose units must be present to act as nuclei for the addition of new chain units.

Enzymatic Degradation of Starch.—Starch can be hydrolyzed both by the action of acids and by the action of the biological catalysts (enzymes) known as *amylases* or diastase. In the animal body, starch-splitting enzymes are present in the highest concentration in pancreatic juice. The importance of these enzymes will be discussed in detail later (Chapter XXIV). Diastase is produced during the sprouting of cereal grains. For example, malt, produced from sprouted barley, has a high content of diastase. It also can be isolated from sprouted wheat.

A commercial method of preparing diastase is by the action of the Aspergillus fungi on wheat bran.

Diastase has been separated into two components. *α-Amylase,* the dextrinizing or solubilizing component, hydrolyzes the starch molecule near the center, and the fragments produced are hydrolyzed again in this fashion until the fragments are small enough to be soluble in water. Only a small amount of maltose is produced by α-amylase. The other factor is *β-amylase,* the saccharogenetic or sugar-producing component. Its mode of action is to hydrolyze off maltose units from the ends of the starch chain. One method of separating the two components depends on the fact that when an aqueous extract of germinated barley adjusted to pH 6 to 7 is heated to 70° C. for fifteen minutes, the β-amylase is destroyed and the α-amylase remains. When a similar extract is cooled to zero degrees and brought to pH 3.3 by adding hydrochloric acid, the α-amylase is inactivated. Crystalline β-amylase from sweet potatoes was isolated in 1948. The amylase in human saliva is almost entirely α-amylase. The formation of dextrins (hydrolytic products of starch) by α-amylase is followed usually by the color that the various dextrins yield with iodine. The color is dependent on the particle size of the dextrins. The following scheme illustrates the series of dextrins formed and the color that each gives with iodine:

Starch →	Amylodextrin →	Erythrodextrin →	Achroodextrin
deep blue	bluish red	red	colorless

These dextrins also can be produced by the action of acids on starch.

β-Amylase, acting on soluble starch, is unable to carry the hydrolysis further than 55-68 per cent conversion to maltose. The residual substance still will give a blue color with iodine.

Uses of Starch.—Cornstarch is used for the production of corn syrup. The wet starch from the starch tables is employed in the preparation of this product. The starch is added slowly to a dilute solution of hydrochloric acid in large tanks known as converters. The hydrolysis is carried out under 30 pounds steam pressure and is allowed to proceed until about 40 per cent of the dry weight of the solids is D-glucose. When the conversion has reached the desired point, the acid is neutralized with sodium carbonate or soda ash. After neutralization, the syrup is filtered through decolorizing charcoal and evaporated under reduced pressure to the desired consistency. The addition of cane sugar syrup and a small amount of flavoring to this product completes the preparation of the familiar corn syrup, or "Karo," used in the home. The cane sugar is added to increase the sweetness. Accordingly, corn syrup, as it reaches the consumer, contains D-glucose (dextrose), maltose, sucrose, dextrins, and a small amount of flavoring.

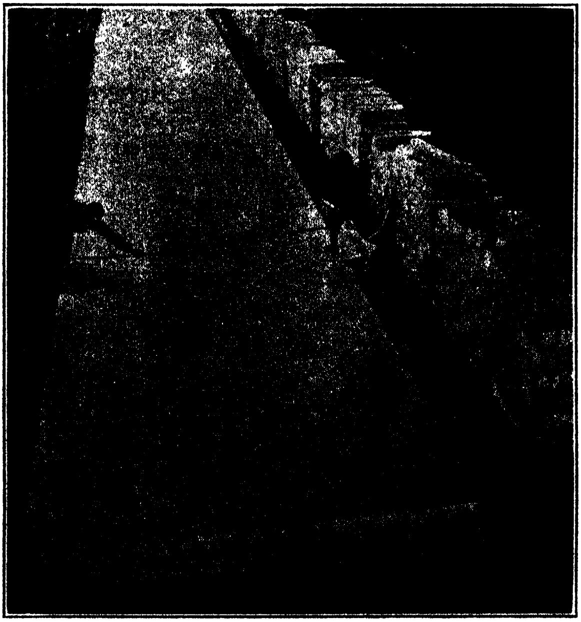


Fig. 52.—Workers wire cutting "70" dextrose sugar slabs. This crude sugar made from cornstarch contains approximately 70 per cent dextrose (D-glucose) and the remainder dextrins and moisture. Two batches of sugar of about 75,000 pounds each are in view. The sugar table measures 110 feet in length, 12 feet 8 inches in width, and holds a batch of sugar 7 to 8 inches deep. This form of crude dextrose is used in the tanning, brewing, and vinegar industries. (Courtesy of Corn Industries Research Foundation.)

The annual consumption of corn syrup in the United States is about a billion pounds. About half of this amount is used in confections, about 300,000 pounds are made into table syrup, and about 50,000,000 pounds are used by bakers in cakes and frostings. About an equal amount is consumed in the manufacture of beer and ale. Jam, jelly, and preserve manufacturers use a slightly smaller amount, while the production of ice cream consumes about a million pounds. The remainder goes into miscellaneous food, technical, and industrial uses. Corn syrup is especially valuable in candy making, since it retards the formation of large crystals. It is also a common component of formulas for the feeding of infants.

For the manufacture of corn sugar, or D-glucose, the process is very similar to that used in preparing corn syrup. The chief difference is that the hydrolysis is continued until about 90 per cent of the starch has been converted to D-glucose. Neutralization, filtration, and concentration are similar in the two processes. The evaporated corn syrups are run into large pans or molds, where they are seeded with crystals of D-glucose and allowed to stand until they set into solid cakes. These cakes are cut by means of wire into large slabs, which are stored for curing or hardening. Sugars of this type contain dextrins, which give them a light brown color. For this reason, they are called "70" or "80" sugars, the figure representing the approximate percentage of D-glucose, the remainder of the product being dextrins and water. These crude sugars are used in the tanning industry to impart properties that aid in the cutting of leather for the manufacture of shoes. This crude D-glucose is used also in the vinegar and brewing industries.

The process for the manufacture of purified crystalline D-glucose is similar to the process for the production of cane sugar. The syrup is concentrated under a vacuum in order to prevent the formation of a dark color due to caramelization. The final crystallization of the D-glucose is carried out in huge cylindrical tanks provided with a spiral agitator that prevents the formation of large crystals and lumps. This final crystallization process requires from six to ten days. In the final step the sugar crystals are run into a rapidly revolving centrifuge, lined with fine mesh copper screen through which the molasses, or hydrol, is ejected, leaving crystals of refined D-glucose. This sugar is washed once with a small amount of water. The final product is a white, refined sugar that may be from 99.5 to 99.8 per cent pure D-glucose.

The use of starch to improve the appearance of clothes in laundering is familiar to everyone. The hot iron in passing over the starched fabric converts the starch to dextrins which adhere to the cloth, are stiff, and give a glossy appearance to the cloth. Large quantities of starch are used for sizing paper: i.e., to fill the pores and give it a better surface. In 1947, it was estimated that the paper industry used annually more than 250 million pounds of corn starch in sizing and finishing paper and another 100 million pounds as an adhesive in the manufacture of paperboard. Another use of starch is as a filler in low grades of soap. Rice starch is a component of talcum powders. Much starch is used in the textile industries as a sizing material. "Thin-boiling" starch, which has a low viscosity and is produced by the action of dilute acids, is best suited for this purpose. The sizing of a yarn with starch makes for easier and better spinning, because the loose fibers on the thread are held in place. Such treatment facilitates the use of the yarn in the spinning machines and the reduction of abrasion during the spinning process.

Starch is used in the manufacture of dextrins, often called British gums. These dextrins are produced by heating dry starch, often sprayed with a small amount of hydrochloric acid, in large metal tanks equipped with a slowly moving stirrer. This device keeps the material from sticking to the sides and bottom while the dampened material is being heated. The time of heating depends upon the product desired. It may be as short as two hours for white dextrins and as long as fifteen hours if a gum is being made. The finished dextrins are powders of colors varying from white to a light yellow. Dextrins are used for wood veneer glue, labels, stamps, and for the pasting of cardboard boxes. Dextrins made from sago starch usually are used as the adhesive on envelopes and stamps, since these kinds of dextrin are much less hygroscopic and have a less objectionable taste than dextrins from other sources.

Starch is used as a filler in baking powders. If the active ingredients of baking powder were not diluted, the housewife would have to make very accurate measurements on very small amounts of this leavening agent in order to obtain successful baked products. Cornstarch usually is employed for this purpose.

Glycogen.—Glycogen, or animal starch, is rarely found in green plants, but it is the reserve carbohydrate that is stored principally in the liver and muscles of animals. Oysters and other mollusks contain a relatively high percentage of glycogen.

Glycogen usually is isolated from liver, often by extraction with hot 30 per cent potassium hydroxide. It differs from starch in that it is soluble in *cold* water, does not gelatinize on being heated in water, and gives a red-brown color with iodine. It does not occur in the form of characteristic granules. Like starch, glycogen does not reduce Fehling's solution, and on acid hydrolysis it yields only D-glucose.

The structure of glycogen is similar to that of amylopectin in that the glucose units are linked preponderantly by α-4-glucoside bonds with branching through α-1,6-linkages. The principal difference is that glycogen is much more highly branched; in fact, multiple branching is thought to be present. The outer branches are thought to be 6 or 7 glucose units in length with about 3 glucose units between branching points. Glycogen's characteristic properties of high water solubility, nonretrogradation, and low digestibility are understandable if it contains such a highly ramified structure. There is no general agreement on the molecular weight of glycogen; values as high as 1,000,000 have been reported.

The glycogen in muscles plays an important part in the series of reactions involved in muscle contraction. The stored glycogen in the liver acts as the reserve carbohydrate by which the glucose content of the blood is maintained at its normal level. These functions will be discussed in detail in Chapter XXIV, Carbohydrate Metabolism.

Inulin.—Another important reserve hexosan is inulin. This polysaccharide is found in the roots of dahlias, Jerusalem artichokes, dandelions, and the roots of the ti plant, which grows in the Hawaiian Islands. Inulin is the only naturally occurring polysaccharide in which the monosaccharide unit contains a butylene oxide, or γ-lactone, ring. On the basis of the methylation studies of Haworth and his co-workers, inulin is thought to contain 30 fructose units in the molecule. Inulin is a white powder that dissolves in hot water to give a colloidal solution. It does not gelatinize on heating, nor does it give a blue color with iodine. Diastase does not hydrolyze inulin, but it is split by the enzyme inulinase, or by dilute acids, to form D-fructose. Inulin does not reduce Fehling's solution.

The inulin of Jerusalem artichokes has been shown to be a commercially feasible source of carbohydrate for the production of butyl alcohol, ethyl alcohol, and acetone by fermentation with microorganisms. The same proportion of these solvents is obtained as in the fermentation of cornstarch by the same organism.

Cellulose.—Cellulose is one of the most widely distributed of all organic compounds. Like starch, it has the empirical formula $(C_6H_{10}O_5)_n$. Starch, glycogen, and inulin often are referred to as the storage polysaccharides, while cellulose is termed the structural or framework polysaccharide. It occurs most prominently in the cell walls of plants. In plants it serves a variety of purposes, such as giving strength and rigidity to the stems, thus aiding the plant in maintaining its upright position. It also serves as a protective agent, as exemplified by bark and the coverings of fruits. In addition, the parts of the plant that are used for transportation of water and food materials are composed of cellulose.

Cellulose is insoluble in water, alcohol, ether, chloroform, and other organic solvents. It is soluble in Schweitzer's reagent (made by agitating copper powder or copper hydroxide with concentrated ammonium hydroxide). Cellulose also is taken into solution by a mixture of one part of zinc chloride and two parts of hydrochloric acid.

Cellulose can be separated into three components. α-Cellulose is insoluble in cold 17.5 per cent sodium hydroxide; β-cellulose is soluble in 17.5 per cent sodium hydroxide and is precipitated on acidification with acetic acid; and γ-cellulose is the portion that remains in solution after precipitation of the β-cellulose.

α-Cellulose is the component that is used in industry for the preparation of cellulose derivatives. Industrial sources of α-cellulose are:

	Per cent α-cellulose
Cotton	87-91
Wood	50-55
Cereal straws	35

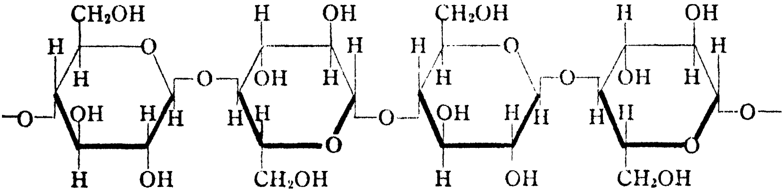
Jute, hemp, flax, and sisal contain a high percentage of cellulose, but they are not used as common sources of the polysaccharide.

Fig. 53.—Bringing cotton to the gin, Lehi, Ark. Cotton contains a higher content of α-cellulose than does any other common natural material. (Courtesy of Farm Security Administration.)

Man is unable to utilize cellulose for food because there is no enzyme in his digestive tract that can hydrolyze it. A certain amount of cellulose in the diet is desirable, since it aids in peristalsis and in the elimination of food residues. Cellulose is utilized by herbivorous animals, such as ruminants, which have more than one stomach. Microorganisms in the intestinal tract of these animals decompose the cellulosic material to products that are digestible. Similarly, termites are able to live on a diet of wood, because protozoa, and possibly other microorganisms living in their intestinal tract, hydrolyze the cellulose into compounds that can be utilized as food by the insects.

Structure of Cellulose.—Cellulose is difficult to hydrolyze, but long boiling with dilute hydrochloric acid under pressure yields almost the theoretical quantity of D-glucose. Hence, like starch, cellulose is composed of D-glucose units, but these units are linked in a different fashion.

A clue to the structure of cellulose is obtained when cellulose is heated with acetic anhydride in the presence of some sulfuric acid. The octa-acetate of cellobiose can be isolated from the products of the reaction. This indicates that cellobiose is the disaccharide unit of cellulose. Further evidence in support of this view is the isolation from cellulose of cellotriose, cellotetrose, and cellohexoses containing, respectively, 3, 4, and 6 molecules of cellobiose. These compounds, obtained by the action of concentrated hydrochloric acid on cellulose, are crystalline, have sharp melting points, and are dextrorotatory. If sections of the cellulose molecule of this size are composed of cellobiose units, it seems reasonable to assume that the remainder of the molecule is constituted similarly. The following structural formula represents a portion of the cellulose molecule:



A portion of the cellulose molecule

X-rays have been a useful tool in elucidating the structure of cellulose. For the theory and method of these x-ray studies, the student is referred to advance treatises on the subject.* In its simplest terms the method consists of passing a beam of x-rays through the material, and allowing the emerging x-rays to impinge upon a photographic plate. Deviations in the path

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*Clarke, G. L.: *Applied X-Rays*, ed. 3, New York. 1938, McGraw-Hill Book Co.

of the x-rays due to their "reflection" by atoms in the material give a pattern from which the expert can calculate interatomic distances. Crystalline substances in which there is a definite recurring grouping of atoms give characteristic patterns on the x-ray photograph. The results obtained by the use of x-rays demonstrate that cellulose gives a pattern characteristic of a crystalline substance.

The theory of the arrangement of the cellulose molecules in fibers that is most favorably received at the present time is the one proposed by H. Mark. According to this concept, the fiber consists of two distinctly different states of aggregation, or orientation, of the molecule. In the fiber there are regions in which the chain molecules of cellulose are highly associated, or aggregated, in a definite fashion so that they give a crystalline pattern with x-rays. These crystalline regions, known as crystallites, are highly oriented in the direction parallel to the fiber axis. Investigations show that water and dilute aqueous solutions do not alter the x-ray pattern of the crystallites. These portions of the cellulose chain contain 150 to 200 glucose units.

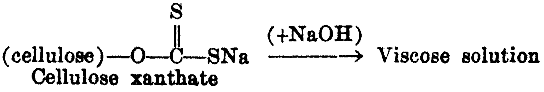
There are, however, according to Mark's concept, other parts of the fiber in which the long-chain cellulose molecules have a completely random arrangement, characteristic of an amorphous material. The absorption of water and the slight degree of hydrolysis that takes place with very dilute acid are due to the amorphous portions of the cellulose molecule. Experiments have shown that the relative amounts of these two phases do not remain constant during chemical and mechanical treatment of the fiber. For example, if a swollen cellulose acetate fiber is stretched, more of the crystalline phase is formed, and there is less of the amorphous stage than was present originally.

At the present time most authorities believe that the cellulose molecule contains about 3,000 glucose units, corresponding to a molecular weight of, roughly, 500,000. There is a variation in chain length, so that this represents an average figure. Most of the work on the structure of cellulose has been done on cotton fibers.

Cellulose Derivatives.—A large part of the consumption of cellulose is in the form of chemical modifications or derivatives. As a result of intensive industrial research, a number of new products have been developed. By clever advertising, a market has been created for these derivatives, and large amounts of cellulose now are being used for the manufacture of these products. One of these is rayon. There are three principal methods for making rayon: the viscose process, the cellulose acetate process, and the cuprammonium process.

Viscose Process.—Over 65 per cent of rayon is produced by the viscose process. The reason for the widespread use of this method is that it utilizes inexpensive raw materials, such as wood pulp, which serves as the source of α-cellulose, sodium hydroxide, carbon disulfide, sodium sulfate, and sulfuric acid. Sheets of wood pulp, usually made by the sulfite process from spruce wood, are soaked in 18 per cent sodium hydroxide. During this soaking period the β- and γ-cellulose are dissolved, and the α-cellulose, which constitutes about 86 per cent of the pulp, remains. After the soaking, the sheets are squeezed dry and are put through a shredder, which reduces the alkali cellulose to soft crumbs. A carefully weighed amount is charged into a water-jacketed churn. After a few minutes of mixing, carbon disulfide is added, and the churn is rotated for two hours. By this process orange-colored cellulose xanthate is formed. The excess carbon disulfide is removed, and the cellulose xanthate is emptied into a mixer and dissolved in dilute sodium hydroxide. The solution that results is very viscous, from which property the process receives its name. The chemical reactions taking place can be represented by the following equations:

$$\underset{\text{Cellulose}}{(C_6H_{10}O_5)_n} + NaOH \rightarrow \underset{\text{Alkaline cellulose}}{(\text{cellulose})ONa} + H_2O \xrightarrow[(+CS_2)]{\text{(steeping process)}}$$



$$\underset{\text{Cellulose xanthate}}{(\text{cellulose})\text{—O—}\overset{\overset{\displaystyle S}{\|}}{C}\text{—SNa}} \xrightarrow{(+NaOH)} \text{Viscose solution}$$

The viscose solution that results from the foregoing process is stored in tanks for two to five days for aging. Then it is forced through the very small openings in spinnerettes. The diameters of these openings, as well as the number in each spinnerette, are different, depending on the kinds of yarn being produced. Each small stream, which is ejected from the holes in the spinnerette, is coagulated on coming in contact with the solutions surrounding the spinnerettes. These small coagulated streams of material are known as filaments. The coagulating bath, which precipitates, or regenerates, the cellulose from the viscose solution, contains 9 to 11 per cent sulfuric acid, 1 per cent zinc sulfate, 4 to 10 per cent glucose, and about

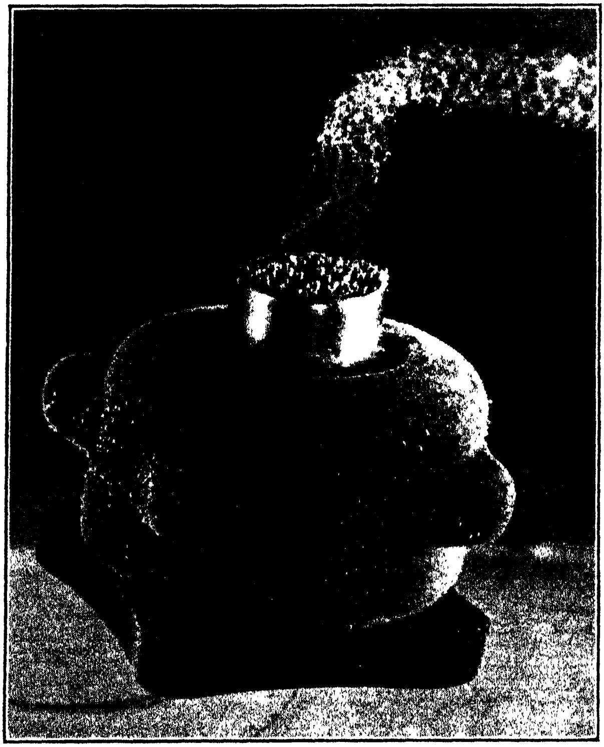


Fig. 54.—A spinnerette in action. Viscose solution is being forced through tiny holes in the thimblelike nozzle into the surrounding acid-coagulating bath. All the filaments are collected together to form a single thread, which, after processing, is ready for the manufacture of rayon fabrics. (Courtesy of Industrial Rayon Corporation.)

20 per cent sodium sulfate. All the filaments from one spinnerette are combined to form a thread, which is wound onto a bobbin or drum. During the coagulation, part of the sulfur of cellulose xanthate is liberated as hydrogen sulfide and must be removed by an efficient ventilation system. Part of the sulfur remains as elementary sulfur and is removed by treatment with sodium sulfide. The thread on the bobbin is washed with sodium carbonate solution, perhaps bleached with chlorine water, washed with more water, and then dried. This material is rewound onto cones, during which process the thread is given a twist. The production of one ton of viscose rayon requires 2.4 tons of sodium hydroxide, 0.7 ton of carbon disulfide, three tons of concentrated sulfuric acid, and about 2.4 tons of wood pulp.

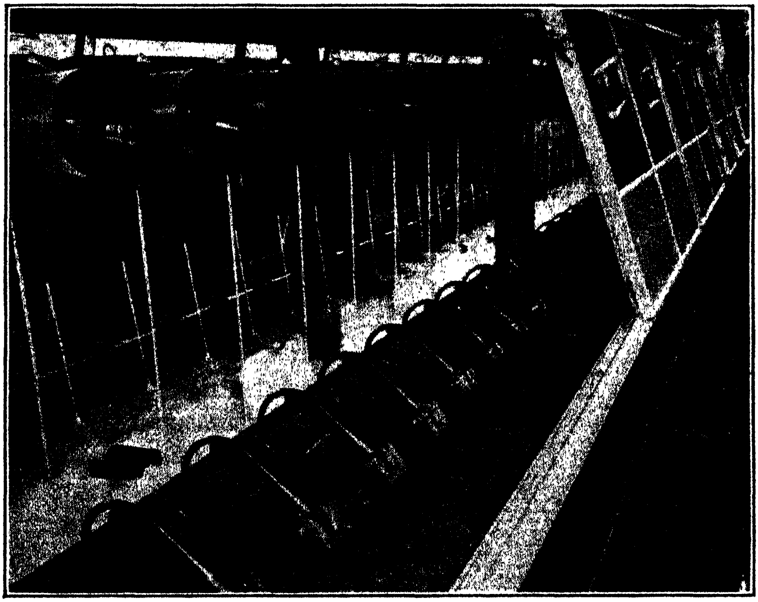


Fig. 55.—A step in the manufacture of viscose rayon. The coagulated filaments that form each thread are being drawn up to a revolving reel. On this reel the yarn is advanced from the back to the outer end, off which it drops through a slot to be processed further by machinery in a lower section. (Courtesy of Industrial Rayon Corporation.)

Cellophane is made mainly by the viscose process, though some is made from cellulose acetate. Cellophane has the same chemical composition as rayon, the difference being that for the manufacture of cellophane the viscose solution is extruded into the coagulating bath through a thin slot. The sulfur is removed by passing the sheet through various solutions, after which the cellophane is drawn through a glycerol solution from which it absorbs glycerol to the extent of about 17 per cent. This glycerol content renders the cellophane pliable. The addition of clear lacquers makes cellophane waterproof. The production of cellophane has increased enormously within the last decade. The increased volume of sales has made possible more than eighteen reductions from the original price of cellophane, which was about $2.65 per pound in 1924, to a price of about 35 cents per pound in 1941.

The use of cellophane as a wrapping material has become very popular. A wide variety of articles, varying from food to wearing apparel, now come wrapped in cellophane. One real estate dealer even wrapped a new house in cellophane as an advertising feature.

Cellulose sponge is made from viscose by incorporating Glauber's salt (Na_2SO_4) crystals in the viscose and then precipitating the cellulose. The blocks so formed are leached with hot water, which dissolves out the Glauber's salt, leaving cavities.

Cellulose Acetate Process.—Cellulose acetate is prepared by treating cellulose, usually in the form of cotton linters, with acetic anhydride and acetic acid. Such catalysts as sufuric acid, sulfur dioxide, or zinc chloride are employed for the reaction, which is carried out in enameled iron tanks. The almost completely acetylated product of this reaction is hydrolyzed to reduce the acetyl content to from 36 to 41 per cent. This corresponds to about two acetyl groups per glucose unit, since the calculated acetyl content of cellulose diacetate is 35 per cent. At this stage of hydrolysis, cellulose is soluble in acetone, a desirable solvent for the spinning operation. The dissolved acetylated cellulose then is poured into water, whereupon the cellulose acetate precipitates. After washing the flakes free of acid, they are dried and dissolved in acetone to form the spinning solution. The carefully filtered spinning solution is forced downward through the fine holes of a spinnerette into a rising current of warm air, resulting in the evaporation of the acetone, thus forming solid filaments of cellulose acetate. These pass out of the spinning chamber and are wound on a spool. Before the cellulose acetate is sent to the textile weaver, the acetate yarn is twisted, lubricated, and wound on the desired type of shipping packages, such as cones, spools, or skeins.

Cellulose acetate is not like the other types of rayon, since it is not regenerated cellulose, and, therefore, differs chemically, physically, and mechanically from the regenerated cellulose yarns made by the other processes. Certain properties that result from this difference in chemical composition are desirable. The cellulose acetate filaments possess a degree of elasticity which gives the fabrics a marked resistance to wrinkling and creasing. Cellulose acetate has a low water-absorbing capacity. It absorbs about one-half as much moisture as silk, less than one-half as much as wool or viscose rayon, and less than cotton. Stains caused by tea, coffee, fruit juices, and other aqueous liquids are more readily removed, because the low swelling and moisture absorption prevents the stains from penetrating deeply into the fibers. For the same reason, acetate rayon fabrics dry quickly owing to the low affinity of the fibers for moisture. Another advantage is that in the wet state the strength of acetate fabrics is reduced about one-third, while that of the other rayons is reduced about one-half.

Cellulose acetate has certain disadvantages as a textile material. One of these is the ease with which it is saponified in hot alkali; this means that it will be affected by hot strong soap solutions. A property that at first caused trouble is its solubility in acetone and some other organic solvents. Fabrics made of cellulose acetate caused consternation and trouble when they reached the dry cleaners, but cleaners have revised their solvents so that now no difficulty is experienced on account of this property. The solubility of cellulose acetate in acetone has been used to advantage in the production of permanently stiffened fabrics, such as collars and cuffs, which do not require starching. A layer of acetate fabric is incorporated between the cotton or other fabrics or some acetate threads are woven into the cotton interlining. The composite fabric then is moistened with acetone, and a multiple fabric is formed that is stiff and porous to moisture.

Another disadvantage is that cellulose acetate is thermoplastic. In laundering this necessitates using a cool iron on such fabrics in order to prevent glazing of the fabric surface, or even melting and destroying the fiber with excessive heat.

The same types of dye cannot be used for cellulose acetate as are used for the other types of rayon. This inability to use the ordinary types of dye hampered the early success of acetate rayon, but later proved to be more of an advantage than a disadvantage. It fostered the development of dyes for acetate rayon that are indifferent to the other types of fiber. This opened up the possibility of securing a wide variety of effects by cross-dyeing goods containing mixed fibers or yarns.

Acetate rayon with a bright luster is made from a spinning solution containing only cellulose acetate and solvent. Yarns with a dull luster are obtained by adding a small amount of titanium oxide to the spinning solution.

Acetate rayon accounts for about 30 per cent of the total rayon consumption in the United States. It is used both alone and in combination with other fibers to produce a wide range of women's wearing apparel, men's summer suits, household fabrics (such as draperies and upholstery), and collar linings. Two common trade names of this type of rayon are Acele and Celanese.

Cellulose acetate is used in the manufacture of Cel-O-Glass, the trade name of a product formed by coating a wire-mesh base with cellulose acetate. This product transmits the ultraviolet rays of the sun, which is the portion of sunlight that forms the antirachitic vitamin D in the body. This is an advantage since ordinary glass does not transmit ultraviolet light. One of the first uses of this product that was dependent upon this property was as a window material for poultry houses. Another use is for enclosing sun porches for convalescents.

Cellulose acetate is less inflammable than the other types of rayon, and for this reason it has been used in the manufacture of film, especially the safety film used for home movies.

Large quantities of cellulose acetate are used in the manufacture of plastics.

Cuprammonium Process.—In the cuprammonium process the cellulose is dissolved in an ammoniacal solution of copper hydroxide. In one process the cellulose is cooked with sodium hydroxide and copper sulfate, after which ammonium sulfate is added slowly. The solution that results is forced through spinnerettes into water, and the filaments as formed are stretched 40 to 60 per cent. Then they enter an acid-coagulating bath of dilute sulfuric acid, which regenerates the cellulose. In this form the fiber no longer can be stretched. The process requires complex machinery and very careful temperature control. It is only because of the possibility of "stretch spinning" that cuprammonium rayon can compete at all with the other processes for making rayon. The thread formed by this process is much finer than that produced by the other processes and possesses the greatest softness. Only about 3 per cent of the United States rayon production is made by the cuprammonium process.

Cellulose Nitrate.—Although cellulose nitrate was the first important derivative of cellulose, and was used by Chardonnet in 1886 to produce the first artificial silk, its use for rayon has been supplanted by the other more economical processes. The production of rayon from cellulose nitrate was discontinued in the United States about 1934. However, cellulose nitrate has many industrial uses and still is made in large quantities. For its production, cellulose, in the form of cotton linters, is nitrated with a mixture of nitric and sulfuric acids. As for the chemical reaction involved, the formation of cellulose nitrate is an esterification reaction analogous to the formation of nitroglycerin. In the cellulose molecule 3 hydroxyl groups per glucose unit are free, so that 3 nitro groups is the maximum number that can be introduced. This would give a cellulose nitrate product with a nitrogen content of 14.16 per cent.

Cellulose nitrate containing more than 13 per cent nitrogen usually is referred to as guncotton, or pyrocotton, since it is used in the manufacture of smokeless powder. This form of cellulose nitrate is unsafe to store or ship. It should be kept wet with alcohol. For the production of guncotton the cellulose is nitrated in iron or stainless steel tanks with a nitrating mixture of 20 per cent nitric acid and 60 per cent sulfuric acid. The time of nitration is about thirty minutes. After nitration the cellulose nitrate is centrifuged to remove excess acid. Next there follows washing for forty hours with hot and cold water. Then the material is boiled with sodium carbonate solution, after which it is given at least ten washings with cold water. The washed material is dehydrated in hydraulic presses, and the resulting block is broken into small pieces, which are macerated with a mixture of one part of alcohol to two parts of ether. During this operation diphenylamine is added as a stabilizer. In the succeeding operations the material is subjected to a sequence of preliminary block presses, macaroni presses, and a final blocking press. In the finishing press the block is subjected to a pressure of several thousand pounds per square inch, and is pressed through steel dies to form long spaghetti-like strings. The flexible ropes of powder are led over cutting machines, which are adjusted carefully to give the exact length of powder grains desired. After the removal of the alcohol and ether by several drying processes, the powder grains are ready for the loading of shells.

Although cotton linters have been used almost exclusively for the preparation of guncotton, under the emergency conditions of World War II wood pulp was substituted for part of the cotton linters. On explosion of guncotton the decomposition products are all colorless gases: carbon monoxide, carbon dioxide, water, hydrogen, and nitrogen; hence, the material was given the name smokeless powder.

If the concentration of acid and the time of nitration are varied so as to give milder conditions, fewer nitro groups are introduced into the molecule. The resulting form of cellulose nitrate, containing about 10 per cent nitrogen, is soluble in mixtures of alcohol and ether and other organic solvents, such as amyl acetate, butyl acetate, and ethyl acetate. It is known as pyroxylin.

Pyroxylin is used as a coating material for fabrics. Coat after coat of pyroxylin can be applied to a fabric, after which the surface can be stamped with a suitable design to make it simulate leather. Such material is used for washable, waterproof upholstery for furniture, for book bindings, for baby carriages, and as a covering for luggage. The trade name of the product of this type manufactured by Du Pont is "Fabrikoid."

Collodion is a 3.5 per cent solution of pyroxylin in a three to one ethyl alcohol-ether mixture. From this are made collodion bags used for dialysis. Another use of collodion is to protect the surface of wounds. For this purpose the material is sold under the trade name "New Skin."

Pyroxylin containing 10.5 to 11.5 per cent nitrogen is heated with camphor to form celluloid. The camphor was obtained mainly from Japan before 1933, but now it is made synthetically from turpentine obtained from the pine trees and pine stumps left after lumbering operations in the southern states. This type of cellulose plastic is used widely because of its great toughness, water resistance, ease of molding, and its availability in a wide variety of transparent, translucent, and opaque colors. One trade name of this product is Pyralin. The principal disadvantage of this material is its inflammability, but within recent years this has been considerably reduced by the use of special plasticizers containing chlorine and phosphate as fire retardants. This cellulose nitrate plastic is the favorite material for fountain pen barrels because of its resistance to the action of the chemicals in ink. Due to its clarity and water resistance, it is also the pre-eminent material for making unbreakable watch crystals. Toilet ware, combs, and buttons are other articles made from it.

Perhaps the largest use of pyroxylin is for the preparation of lacquers. The cellulose nitrate in lacquers contains approximately 12 per cent nitrogen. After nitration the product is heated with water under pressure so as to modify the nitrated cellulose in order that a larger quantity can be dissolved and yet yield a solution thin enough to be applied with a spray gun. If the pyroxylin and solvent were the only components of the lacquer, the film left after evaporation of the solvent would wrinkle and buckle away from the surface being coated. In order to overcome this defect, substances known as plasticizers are added. These substances will not volatilize when the film dries, and the film remains plastic. Some of the plasticizers are tricresyl phosphate, tributyl phosphate, dibutyl phthalate, and castor oil. Frequently used solvents for cellulose nitrate lacquers are ethyl acetate, butyl acetate, amyl acetate, ethyl lactate, and the glycol derivatives. Probably the largest single use of nitrocellulose lacquer is as a finish for automobile bodies. It also is used as a coating for refrigerators, by the use of which the cost of finishing a refrigerator has been reduced from four cents per square foot eighteen years ago to one cent per square foot in 1941. Ocean liners, streamline trains, boats, furniture, and interior woodwork in homes have been finished with this lacquer. Formerly, cellulose nitrate lacquer was much used as a protective coating for airplanes, but because of its ease of ignition and inflammability, it is being replaced by cellulose acetate and more recently developed derivatives, such as cellulose acetopropionate and acetobutyrate.

Ethyl and Methyl Celluloses.—Another group of cellulose derivatives are the ethers. The most important of these is ethyl cellulose (Ethocel). The first step in its manufacture is the formation of an alkali cellulose. Ethyl cellulose is produced by the action of ethyl chloride and excess alkali on cellulose in reactors at about 200° C. The product then is washed to remove salt and excess alkali. Among the many important applications of ethyl cellulose are its use in lacquers, varnishes, and adhesives to improve toughness. It also is used extensively for molded plastics of all sorts.

Methyl cellulose is made by the same general method as is the ethyl derivative. An unusual property of methyl cellulose is that of being more soluble in cold than in hot water so that solutions become more viscous as the temperature is raised.

Since it is nontoxic, methyl cellulose is useful for thickening food products, in cosmetic preparations, in dentifrices, in pharmaceuticals, and as a base for salad dressings.

Oxidized Cellulose.—A recent cellulose derivative of interest is *oxidized cellulose.* It is produced by the controlled oxidation of cellulose with nitrogen textroxide. This reagent has the property of acting selectively on the free primary hydroxyl groups on the number six carbon atom of the glucose units to convert them to carboxyl groups. Oxidized cellulose has found use as surgical gauze and bandages, where use is made of its solubility in the slightly alkaline fluids of the body.

Textile Fibers.—Rayon is not merely a substitute for silk; it is a textile fiber with characteristic properties of its own. Rayon has an advantage over natural fibers in that its properties are controllable. For example, the fibers can be spun to any desired size, the yarn can be made to have either a high luster or a dull appearance, and, more important than these, the quality is constant. Natural fibers of wool, silk, and cotton vary in their properties with the climate, season, and health of the plant, animal, or insect producing the fiber. Formerly, rayon yarns had the disadvantage that they lost about 50 per cent of their strength when wet, but now, for some special uses, rayon yarns of increased strength are being produced by applying tension on the liquid filaments before complete coagulation has taken place. Du Pont's "Cordura" is an example of this type of modified yarn. It is used in sails, in bus and truck tires, and in tires on the landing gear of airplanes.

A new form of rayon yarn, known as spun rayon, was developed in 1937. In order to understand its manufacture and properties, it is necessary to consider classes of textile fibers.

The major textile fibers can be classed as (1) the continuous filament fibers, such as silk; and (2) the relatively short fibers, often called staple fibers. Cotton, linen, and wool are all examples of the short-fiber type. In order to make yarn out of the continuous filaments, the desired number of filaments must be laid side by side and twisted to form a thread. To make a textile yarn from staple fibers, a rather intricate technic involving carding and spinning is required. The most common form of rayon, and the only kind produced before 1937, was made from continuous filament fibers. Spun rayon, on the other hand, is made from fibers corresponding in length to staple fibers.

In the production of spun rayon the yarn is made from the same spinning solutions as those used for the continuous filaments, but the spinnerettes in the process have at least ten times as many openings. The large number of filaments that form in the coagulating bath are united to form a "rope." In the so-called "dry process' this large bundle of fibers is processed, dried, and cut into the desired lengths. These are blown into a fluffing machine in which a rapidly revolving wheel separates the mass, leaving the short lengths of fibers curled and intermixed in all directions. This fluffed, cut rayon is baled in a manner similar to cotton.

In the so-called "wet process" the filaments from a number of jets are collected together and are drawn off as a continuous tow or rope. This rope is run directly to the cutter while it is still wet. The cut material is processed in bulk. This wet system allows the cut raw staple to contract and crimp during the processing, giving it a spinnability more like that of cotton.

One reason that spun rayon has achieved such wide acceptance is that it is much less expensive than the continuous filament rayon, since the processing, bleaching, and drying all can be done on a much larger scale, thus making possible tremendous productions at a minimum labor cost. A pound of staple yarn for making spun rayon can be put on the market for about one-half the cost of a pound of the continuous filament yarn. Also, cut staple rayon fibers have the advantage over natural staple fibers in that they are more uniform, both as to length and size, and can be made to any desired fiber specification by the spinner. Rayon staple gives a much softer, more pliable yarn than cotton. The fiber size and staple length of the spun rayon are not only more uniform than any of the natural fibers, a fact that makes yarn spinning more economical, but also the filaments can be spun from bright, semidull, or dull material, so that the possibilities of variety of construction are almost limitless.

Staple-length rayon can be spun on the machines used for the natural staple fibers. Although the principles of spinning are the same for all staple fibers, differences in diameter, length, and other physical properties have resulted in the development of machinery particularly suited to each kind of staple fiber. For example, the machine for cotton is designed to handle fibers that are 0.75 to 2.0 inches in length. The machinery for wool is adapted to fiber lengths of 2 to 4 inches. Staple rayon fibers of lengths corresponding to cotton and wool fibers can be woven on machines used to weave the natural fibers.

Nylon.—One of the most familiar of the synthetic fibers is nylon. Nylon is the generic name for a group of polymeric amides formed from dibasic acids and diamines. Currently the usual type of nylon is made from the mutual reaction and polymerization of adipic acid ($HOOC(CH_2)_4COOH$) and hexamethylenediamine ($H_2N(CH_2)_6NH_2$). Adipic acid and hexamethylenediamine are produced from benzene by a series of transformations.

Benzene → Phenol → Cyclohexanone → Adipic acid → Adipamide →
Adiponitrile → Hexamethylenediamine

Recently the Du Pont Company began the production of hexamethylenediamine from furfural (see page 508).

In the manufacture of the common type of nylon, a salt of adipic acid and hexamethylenediamine is formed by combining equimolecular proportions of these substances. Condensation, during which water is split out, and polymerization are accomplished by heating the salt in an autoclave at temperatures ranging from 200 to 300° C. The type of structure present in the polymer can be indicated as follows:

$$HOOC(CH_2)_4CO\text{—}[NH(CH_2)_6NH\text{—}CO(CH_2)_4CO]_n\text{—}NH(CH_2)_6NH_2$$

The resulting compound is a polyamide, somewhat similar to proteins in its structure, in that it contains the peptide linkage. This is the characteristic type of linkage of the constituent amino acids in proteins (see page 559).

The valuable properties of nylon arise from the unusual regularity of its long chainlike molecule. This molecular arrangement is sufficiently regular for it to give an x-ray pattern of a crystalline substance. Because of the low solubility and the high stability of this polyamide, nylon fibers are formed by forcing the melted material at 275 to 285° C. through spinnerettes under conditions of tension so that the solidifying filaments are stretched three to five times.

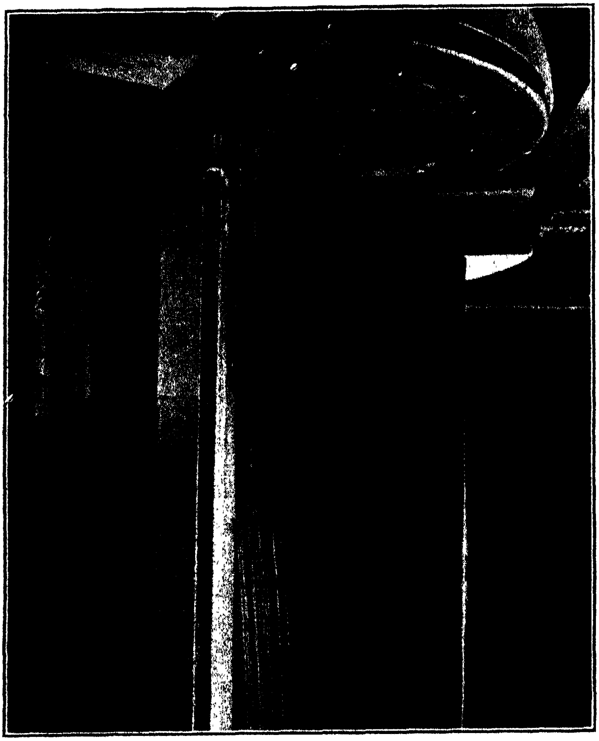


Fig. 56.—The birth of nylon filaments. The polyamide resulting from the condensation and polymerization of adipic acid and hexamethylene diamine is melted at 285° C. and forced through tiny holes in the spinnerette. All the filaments shown here will be wound together to form nylon yarn. (Courtesy of the Du Pont Co.)

Cold-stretching follows spinning. In this step the filaments are gathered together, a lubricant is applied, and they are wound on a bobbin or spool. From this bobbin the yarn is transferred to another bobbin of the same size running four or more times as fast. Thus the yarn is stretched to at least four times its original length, "necking" down to half its former diameter.

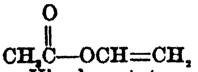
During cold-stretching the yarn becomes highly lustrous and there is a remarkable increase in strength and elasticity. The yarn then is twisted, wound on spools, and baked in ovens to set the twist.

Before the development of nylon for textile use, monofilament (single strand) heavy nylon was used in fish leaders, and as bristles for toothbrushes, hairbrushes, paint brushes, and industrial brushes such as those employed in bottle washing and dry cleaning. A more recent development is the use of the heavy strands for tennis-racquet strings, which are practically unaffected by water and atmospheric conditions, and do not fray or deteriorate on storage of the rackets. Nylon is used for surgical sutures because it has a smooth surface and a low wetability. Nylon thread now is available for home use. Tests show that this thread has greater strength and elasticity than other threads, which property permits garments to stretch under unusual strain without breaking the machine stitching. Nylon rope found many uses during World War II, one of which was as glider towlines.

Nylon fabrics are wetted by water, but the fibers absorb much less water than do other commonly used textile fibers. This property explains why nylon stockings dry rapidly. Nylon hosiery was released to the country on May 15, 1940, and within the first year about 64 million pairs of women's hosiery were sold. Nylon fabrics are not damaged by the fungi responsible for mildew, and they are not attacked by clothes moths.

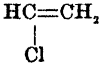
Boat owners have found that nylon offers better tensile strength, lower water absorption, and a smoother surface than other sail fabrics. The manufacturers of women's bathing suits have taken advantage of nylon's quick drying properties. Huge quantities of nylon fabric was used during World War II for the manufacture of parachutes because of the high tensile strength and elasticity of the nylon material.

Vinyon.—Another type of fiber used for fabrics is that made from polyvinyl esters. The material used for textile fibers is a copolymer of vinyl acetate and vinyl chloride.



$CH_3\overset{\overset{O}{\|}}{C}-OCH=CH_2$

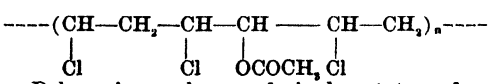
Vinyl acetate



$\underset{\underset{Cl}{|}}{HC}=CH_2$

Vinyl chloride

If vinyl acetate and vinyl chloride are mixed together with a solvent and a catalyst, and heat is applied, the result is a copolymer in which, theoretically, the two materials react with each other at the double bond. The resulting product contains about 88 per cent vinyl chloride and 12 per cent vinyl acetate. The probable structure of the copolymer is thought to be:



$$\text{----}(\underset{\text{Cl}}{\text{CH}}-\text{CH}_2-\underset{\text{Cl}}{\text{CH}}-\underset{\text{OCOCH}_3}{\text{CH}}-\!\!-\underset{\text{Cl}}{\text{CH}}-\text{CH}_2)_n\text{----}$$

Polymeric copolymer of vinyl acetate and vinyl chloride

The average molecular weight of the copolymer, as made into textile fibers, is about 22,000. Vinyon is the trade name for the textile made from this copolymer by the Carbide & Carbon Chemical Corporation.

For the production of the synthetic fiber the copolymer is dissolved in acetone and is formed into filaments by the same process as is used for acetate rayon. The fabric made from vinyon yarn has some very unusual properties. The strength of the yarn is the same in both the wet and the dry states. Water wets the material only when wetting agents, such as detergents, are used. Vinyon fabrics are exceptionally resistant to the action of acids and alkalies. At room temperature the fabric is not attacked by 70 per cent nitric acid, concentrated hydrochloric or hydrofluoric acids, 30 per cent sodium hydroxide, or concentrated ammonium hydroxide. It is also unaffected by alcohols, glycols, and aliphatic hydrocarbons. It is dissolved, however, by ketones, and is partly dissolved by esters, ethers, and certain halogenated hydrocarbons. Due to its high resistance to the action of most chemical reagents, vinyon is being used for the manufacture of filter cloth for chemical solutions. Its resistance to wetting makes it also a prized material for bathing suits.

Fiberglas.—A new development in the manufacture of fabrics is the use of glass fibers. The material, known as Fiberglas, is made both in continuous filament and staple forms. The diameter of the fibers is about 0.00025 inch. Translated into more understandable terms, the filament diameter is about onefifteenth that of a human hair. For the production of Fiberglas, glass of high purity first is melted in an electric furnace from which it emerges through very fine orifices. The fine streams of molten glass are converted into fibers by jets of high pressure steam moving at rifle-bullet speed. The fibers then are gathered on a suitable winder or revolving drum. A small amount of mineral oil is used as a lubricant between the individual fibers to minimize friction, which would tend to cause scratching and breaking. The lubricant can be removed later by washing with soapy water or by extraction with an organic solvent. Both continuous filament and staple glass fibers can be processed on standard textile machinery after slight modifications and adjustments.

The properties of glass in the forms with which we are familiar are transparency, hardness, durability, and brittleness. Glass that is reduced to the form of *very fine* fibers retains these properties, but the brittleness has been reduced until it no longer is of practical consideration. Instead of brittleness, there are flexibility, resiliency, and extraordinary tensile strength The uses to which Fiberglas has been put take advantage of these important properties. One of these uses is in the electrical industry for the insulation of electric motors and generators. Its excellent insulating properties have been utilized in such articles as refrigerators, water heaters, and stoves. Filters made of Fiberglas for air-conditioning systems have proved very successful. Draperies, tapestries, and awnings made of glass fabric are not affected by climatic conditions and are fireproof and heat resistant. A cigarette can burn its length on such a fabric without harmful effects. The stain can be removed with soap and water.

Glass fibers formerly were available in only four permanent glass colors, but a new process of coating glass yarn with a very thin film of a protein such as gelatin makes it possible to dye the yarns with dyes commonly used for wool and silk. Because of their thermal insulating and fireproofing properties, glass fibers bonded with phenolic plastics are being used in railroad passenger and refrigerator cars and in airliners.

Protein Fibers.—Proteins as a source of material for textile fibers are being studied and developed, but as yet this source does not contribute a substantial amount to the textile industry. A recent addition to textile fibers is "Aralac," made from casein. It is more expensive than rayon and cotton, but less expensive than wool and fur. As yet it has not been used as the sole material for fabrics, but it is said to blend well with other textile fibers. It has been used since early 1941 as a part of the felting material in hats.

The process for the manufacture of textile fibers from soybean proteins has been carried out successfully. Most of this work has been done by the Ford Motor Company. It is reported that soybean protein fibers show promise in blends of wool for use in suiting and upholstery fabrics.

A textile fiber made from peanut protein has been developed in England under the brand name of Ardil. Fibers from zein, the protein of corn, have been made on an experimental scale. Lundgren and his associates at the Western Regional Laboratory have prepared fibers from waste egg white and chicken feathers. More work remains to be done on protein fibers to overcome their defect of low tensile strength when they are wet.

Hemicellulose.—About 20 per cent of the weight of wood is a heterogeneous material termed hemicellulose. Under different conditions hemicelluloses may function either as skeletal or as reserve polysaccharides in plants. They are differentiated from cellulose by their marked ease of hydrolysis. They consist of a mixture of sugars, both hexoses and pentoses, in chemical combination; in some cases, uronic acids (sugar acids) also may be present. Because of the great variability in the composition of this material from various sources, as well as its heterogeneity, much confusion exists in the literature concerning this class of carbohydrates. In the pulping of wood for the production of pure cellulose, hemicelluloses are present in the waste cooking liquors. After the removal of lignin these sugars can serve as sources of fermentable carbohydrate for the production of solvents. This process, however, has not been developed industrially to any large extent as yet.

Mixed or Acidic Polysaccharides

Pectic Substances.—Pectic substances belong to the acid polysaccharides, so called because of their high content of uronic acids (sugar acids). A class of pectic substances known as protopectin occurs in the middle lamella of plants as a thickening or incrustation, particularly in the cell walls of unlignified plants. The protopectin from the middle lamella may be very different in composition from the protopectin that occurs in the other parts of the plant. A considerable portion of the protopectin is combined with the cellulose, probably in some cases by actual esterification between the carboxyl groups of the protopectin and the hydroxyl group of cellulose. The protopectin can be hydrolyzed free from the cellulose by the enzyme, protopectinase, or by long-continued heating with water under pressure, or by heating with dilute acids. These treatments convert the water-insoluble protopectin into soluble pectin. This transformation from insoluble protopectin to soluble pectin takes place during the ripening of fruit.

Pectin is water soluble and is the best known of the pectic substances. It is a material with high-molecular weight; it disperses in water to give a viscous, colloidal solution from which it is readily precipitated by alcohol. Pectin contains about 10 to 12 per cent of methyl alcohol combined mainly in the form of methyl esters. On treatment of pectin with 0.1 N sodium hydroxide in the cold or heating with 0.02 N hydrochloric acid, the methyl groups are hydrolyzed off to give methyl alcohol and an insoluble derivative, pectic acid.

Isolation of Pectin.—The common commercial sources of pectin are citrus fruits and apple pomace (peelings and pulp). In citrus fruits the pectin occurs largely in the white peel portion (albedo), which lies beneath the pigmented and oil-containing outer rind (flavedo). Lemon rinds contain 30 to 35 per cent pectin, and apple pomace contains from 10 to 15 per cent pectin, both on a dry-weight basis.

In the newer methods of preparing pectin, the pectin-containing material is heated in water acidified to pH 2-3 and containing 3-5 per cent of a polyphosphate, such as sodium tetraphosphate or sodium hexametaphosphate (Calgon). The aqueous extract usually is pressed from the residue, filtered, and the pectin precipitated, washed with alcohol, and dried. However, there are several methods for the separation of the pectin. In one method it is precipitated with alcohol. In another, it is precipitated with aluminum sulfate and ammonia. In still another, the extract is dried by being sprayed on a heated, revolving drum. In some cases the extract is evaporated and sold as a syrup. The commercial product "Certo" is an example of this type of pectin. These liquid forms contain from 4 to 4.5 per cent pectin.

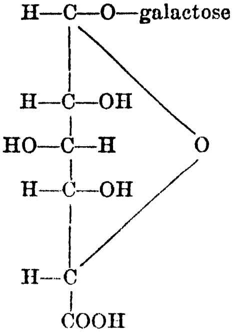
For the formation of an acceptable jam or jelly, sugar (usually sucrose), acid, and pectin must be present in the proper concentrations. Using ordinary unmodified pectin the optimal conditions for the preparation of jellies are from 55 to 65 per cent sucrose, pH 3 to 3.4, and from 0.7 to 1.0 per cent pectin. Commercial jellies must be firmer for shipping, and usually contain about 1.25 per cent pectin. According to Olsen, if we take for granted that pectin is a negatively charged, hydrophilic colloid (and this seems a permissible assumption), then in the formation of a jelly, the sugar acts as a dehydrating agent, and the hydrogen ions from the acid reduce the negative charges on the pectin, thus permitting the latter to coalesce in the form of a network. Gelation is aided by brief boiling in a slightly acid solution because some of the methyl ester groups are split off. Boiling for too long is detrimental since the pectin molecule itself is hydrolyzed and the jelly becomes progressively thinner.

Structure of Pectin.—The present conception of the structure of pectin is that the backbone or principal portion of the complex is composed of a chain of galacturonic acid units. The galacturonide units have the pyranose ring structure and are linked together by glycosidic bonds. The proportion of carboxyl groups of the galacturonide units that are esterified with methyl groups varies widely depending on the source, method of isolation, and treatment of the particular sample of pectin. Although they are essentially polygalacturonides, pectins also contain D-galactans and L-arabans. The relative amount of araban or galactan seems to depend largely upon the source from which the pectin is obtained. Some pectins contain up to 30 per cent arabans while others contain up to 40 per cent galactans. It is fairly certain that the galactan is composed of β-D-galactopyranose units linked by 1,4-glycosidic bonds. The araban, on the other hand, is a branched chain group composed of arabinose units in the furanose form linked together by 1,5-glycosidic bonds. Branching is thought to occur by linkage through 1,2 positions. Just how the arabans and galactans are joined to the main chain is not clearly understood; probably they are held by covalent bonds. It has been shown that the characteristic properties of pectin such as gelation are principally properties of the polygalacturonide chain. The galactans and arabans, often called "ballast materials," act mainly as diluents.

Uses of Pectin.—The largest use of pectin is in the formation of jams and jellies, but, in addition, other uses are being developed as mass production lowers the cost of the product. Pectin is used in hand and face lotions. Bakery products containing pectin retain their moisture and remain fresh longer. Pectin has been used in the quick-freezing process for fruits, especially strawberries, in which it functions to preserve the firmness and the natural color of the fruit. Kutscher and Blumberg reported that the treatment of diarrhea in infants with pectin, agar, and Dextri-Maltose in a whole milk formula is a safe, effective, and satisfactory procedure. It has been found that when pectin is introduced intramuscularly, it exerts a distinct accelerating effect on the coagulation of drawn blood. However, it has no coagulating effect on circulating blood. Kochs found this treatment with pectin to be useful in lung bleeding, ulcerative colitis, and for bleeding in mouth and nose cavities. Pectin as a basis of medicated salves has been successfully used in the treatment of bedsores and ulcers that are difficult to heal.

Within the last few years considerable research has been done on preparing pectins with low methoxyl content without appreciable degradation of the pectin molecule. According to the new system of nomenclature pectins containing more than a negligible proportion of methyl ester groups are called *pectinic acids.* The most suitable methods for de-sterification of pectins to form pectinic acid appears to be by means of the enzyme (pectase) from tomatoes or by the action of ammonium hydroxide at 15° C. One advantage of the low methoxyl pectins is that they make possible the preparation of low solid gels. Such jellies made by using pectinic acids may have a sugar concentration as low as 35 per cent. The concentration of calcium ions is extremely important in the formation of this type of gels. As an example, pectinic acids having methoxyl contents of 3-4 per cent and viscosities of 6-10 centipoises need from 15 to 20 mg. of calcium ions per gram of pectinic acid for gel formation. The importance of calcium ions in gelation affords the possibility of preparing attractive and palatable gels from milk and milk products. Another proposed use for low methoxyl pectin is as a sausage casing or protective film for other foods. The sausage is dipped in a warm solution of low-methoxyl pectin containing calcium ions. The adhering liquid gels on cooling and is dried in a current of warm air. If the coated product is boiled the coating dissolves; if fried, the film may be consumed with the meat since it is tender and edible.

Gums.—The plant gums are substances that yield sugars and related compounds on hydrolysis. Gums, in most cases, are abnormal products formed by plants as a result of injury, disease, or adverse climatic conditions. When dry, gums are rather hard, translucent, amorphous bodies. Most gums are soluble in water, and form sticky, colloidal solutions from which they can be precipitated by alcohol. The natural gums usually are levorotatory, a characteristic that serves to distinguish them from the dextrins which are dextrorotatory. After prolonged boiling with acid, the gums yield mixtures of pentoses, hexoses, and aldobionic acids. The aldobionic acids are uronic acids in which a sugar is linked to the number one carbon atom by a glucosidic type of linkage. For example, galacto-glucuronic acid is a typical aldobionic acid.



Galacto-glucuronic acid

The aldobionic acids give acid properties to the gums. In the plants they usually are present as the potassium, calcium, or magnesium salt of these acids.

One of the gums of commercial importance is gum arabic (acacia). It is obtained from an exudate on the branches of some species of acacia trees. On hydrolysis gum arabic yields galactose, arabinose, and aldobionic acids. Gum arabic is used in the formation of water-in-oil emulsions. During World War I sterile solutions of gum arabic were injected intravenously to increase the blood volume in cases of excessive loss of blood.

Another gum of commercial importance is tragacanth. On hydrolysis it gives arabinose, xylose, galactose, and one of the aldobionic acids. It is used widely in hand lotions.

Mucilages.—The mucilages differ from the gums in that they are normal components of certain plants that possess mucilage-secreting hairs or special mucilage cells. In some plants the mucilage is concentrated in the outer walls. Mucilages adsorb water readily, thereby increasing the hydration capacity of the plant. Mucilages are odorless, tasteless substances that swell markedly in water, forming colloidal suspensions that set to rigid gels on cooling. Agar-agar (agar) is the most common mucilage. The commercial product is the dried and partly bleached extract of certain red algae, more commonly referred to as seaweeds. These grow in enormous quantities, especially on the West Coast of the United States. Agar is the sulfuric acid ester of a complex polysaccharide. The gel formed by agar is not liquefied by the bacteria that liquefy gelatin, and partly for this reason, agar is a frequently used ingredient for the preparation of "slants" for bacterial colonies. Agar is not digestible, and so adds bulk to the food. When it is combined with mineral oil in an emulsion, it functions as an aperient.

Another mucilage is carrageen (Irish moss), which is obtained by extracting the seaweed *Chrondrus crispus* with boiling water. Plymouth County, Massachusetts, and Prince Edward Island, Canada, are important centers of production. Irish moss is used in making blanc mange and other puddings, as a clarifying agent for beverages, and in concentrations of 0.045 per cent as a stabilizer for chocolate in chocolate-milk beverages.

Lignin.—Lignin occurs in the middle lamella and in the cell walls of plants. It will be remembered that these are also the parts of the plant in which pectin occurs. As a rule, however, the two polysaccharides are not found associated to any great extent. Where there is a high content of one, there is little of the other. The importance of lignin can be appreciated better when it is considered that lignin composes from 25 to 30 per cent of the weight of wood. In the manufacture of wood pulp the lignin must be removed. The sulfate, sulfite, and soda processes for the production of wood pulp all are concerned mainly with the removal of lignin.

In the sulfite process wood cut up into small chips is heated for ten hours under 100 pounds of steam pressure in tanks known as digestors. The sulfite cooking liquor, which contains mainly calcium bisulfite, $Ca(HSO_3)_2$, is formed by the reaction of an excess of sulfur dioxide on lime. Under the conditions of the digestion the lignin in the wood is converted to soluble calcium lignosulfonates. In the United States and Canada the waste sulfite liquors resulting from the production of sulfite pulp have been estimated to contain about 2,500,000 tons of lignin, 1,000,000 tons of simple reducing sugars, and 680,000 tons of organic acids per year. For the recovery of lignin sulfonate, the waste sulfite liquors are made alkaline, and the precipitate of lignin sulfonate can be separated in filter presses.

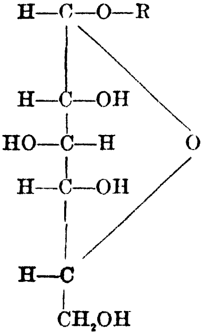
Some of the large quantities of lignin that potentially are available are being used for the production of vanillin and lignin plastics. The vanillin is made by an alkaline processing of lignin sulfonate, followed by extraction with organic solvents and final purification. A large proportion of the vanillin consumed in this country is made by this process.

The soda and sulfate processes employ alkaline cooking liquids. In the soda process this is, essentially, a dilute solution of sodium hydroxide. In the sulfate process the alkaline solution contains sodium hydroxide, sodium sulfate, sodium sulfide, and sodium carbonate. The lignin in the spent liquor from these processes is present as the soluble sodium salt and is precipitated on acidification.

Although many research workers in a number of countries have worked on the structure of lignin for over a hundred years, the problem still is far from being solved. All workers agree that lignin contains methoxyl groups. The estimation of these methoxyl groups has been used to characterize and determine the purity of samples of lignin. In addition, it has been established that phenolic and alcoholic hydroxyl groups are present in the molecule. Vanillin and coniferyl aldehyde have been identified among the decomposition products of lignin. No structure that will account for all the known decomposition products and properties has been proposed that is acceptable to the leading research workers in the field.

Uses of Lignin.—New uses of lignin are being sought because potentially large quantities are available. Combined with other materials, lignin is being used as a roofing material. Also, it has been used successfully as a binding material in road building. The production of vanillin from lignin already has been mentioned. The incorporation of lignin as a part of the negative plates of storage batteries has been found to result in a ten-fold increase of current output in zero weather. The use of lignin as a material for the manufacture of plastics has been investigated. Plasticized with such substances as furfural, it gives a product that can be hot-pressed to give a hard, black, molded product at a low cost. A successful use of lignin is to replace part of the more expensive phenolic resin in the thermosetting types of plastic. Lignin has been used as an agent for removing iron from water for domestic and industrial purposes.

Glucosides.—The methyl glucosides, previously considered (see page 331), are the simplest members of a large group of naturally occurring substances. The general formula of the glucosides can be represented:



α-Glucoside

R denotes the nonsugar group, usually referred to as the aglucone group.

It is obvious that sugars other than glucose can be present in this type of compound. *Glycosides* is a widely used general term that includes all compounds of this general structure regardless of the sugar present. If this general term is used, then the glucosides are a subdivision of this group. However, since the glucosides are by far the most important and most widely distributed class, they will be the only group considered at length.

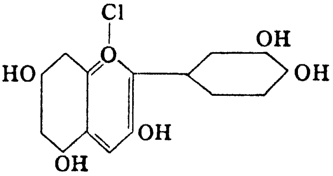
Glucosides usually are obtained from plant materials by extraction with water or an organic solvent, such as alcohol. When water is used as a solvent, the extraction mixture must be heated to the boiling point at the beginning of the extraction in order to inactivate the enzymes normally present; otherwise the glucoside would be hydrolyzed during the extraction. Where glucosides occur in plants, the enzymes that will hydrolyze them usually are present, but not within the same cell. When the plant cell walls are broken by grinding or freezing, the glucoside and enzyme come into contact, and hydrolysis results unless the enzyme has been inactivated. All glucosides are hydrolyzed by heating with an acid, yielding a sugar and an organic residue.

Among the phenolic glucosides is *arbutin*. The aglucone group is hydroquinone (page 441), $OH—C_6H_4—OH$. Arbutin can be isolated from the leaves, bark, and roots of many varieties of pears.

Salicin is a colorless, crystalline, bitter-tasting glucoside that can be isolated from willow bark. On hydrolysis salicin yields glucose and salicyl alcohol. Oxidation of the latter gives salicylic acid, derivatives of which are used for the relief of pain. Aspirin, acetylsalicylic acid, is perhaps the most widely used of these derivatives. Salicylic acid and its salts are used in the treatment of rheumatism, but salicin, when used for this purpose, has the advantages of being less irritating and producing fewer digestive disturbances.

Phlorhizin is a glucoside found most abundantly in the root bark of apple, pear, cherry, and plum trees. It possesses the remarkable property of causing renal diabetes, or artificial glucosuria, when taken internally or when injected subcutaneously. Much of the experimental work on diabetes has been done on phlorhizinized dogs.

Many soluble plant pigments are glucosides. The soluble red, blue, and violet pigments of flowers, fruits, and leaves are glucosides known as anthocyanins. These glucosides on hydrolysis yield a sugar and an anthocyanidin. In some cases, more than one molecule of hexose is obtained, and the sugar may not be glucose. The presence of anthocyanins in plants is responsible for the color of flowers, of foliage plants, and of the brilliant autumnal foliage. In the case of the development of the color in autumnal foliage, the freezing temperatures rupture the cell walls, thus allowing enzymes to hydrolyze the glucosides and set free the anthocyanidin. The low temperature also interferes with carbohydrate metabolism, and this may be another factor in the formation of the pigment. A typical anthocyanidin is cyanidin, which occurs in the cornflower, the red rose, and the deep red dahlia. It is believed to have the following structure:



Cyanidin chloride

The point of attachment of the sugar molecule has not been established definitely. The oxygen in the ring is *basic* and with acids forms oxonium salts in which the oxygen apparently is quadrivalent. The formation of these oxonium salts is utilized in the isolation of the anthocyanins. The wide range of hues in plants likely is produced by variations in the acidity of the cell sap. The anthocyanins act somewhat like indicators, since they form red oxonium salts in acid solution, blue-green salts in neutral solution, and blue salts in alkaline solution. This phenomenon can be observed in the cooking of red cabbage. If the red color is to be retained, a small amount of acid, in the form of vinegar or lemon juice, is added. If cooked in ordinary tap water, the alkalinity will be sufficient to cause the cabbage to turn blue.

Other glucosides that are responsible for the color in flowers and leaves are the flavones and the xanthones. The aglucone group in these compounds is similar in structure to that of the anthocyanins.

Another group of glucosides is the cyanophoric, or cyanogenetic, glucosides, characterized by yielding hydrocyanic acid on hydrolysis by acid or the appropriate enzyme. The cyanophoric glucosides are distributed fairly widely and are present in several forage plants of economic importance. ***Amygdalin*** is one of the best known of these glucosides. It occurs in the seed of the bitter almond and in the kernels of plums, peaches, prunes, and apricots. Hydrolysis by acids or by the enzyme emulsin yields benzaldehyde, hydrocyanic acid, and two molecules of glucose.

Dhurrin is a cyanogenetic glucoside present in sorghum, millet, and Sudan grass. On hydrolysis it yields p-hydroxybenzaldehyde, hydrocyanic acid, and two molecules of glucose. The hydrocyanic acid content of this glucoside is responsible for the annual loss of a large number of livestock. The cured hay from these forages is not toxic, but under certain conditions and stages of growth one plant may contain a lethal dose of hydrocyanic acid. Young plants about 3 inches high, sprouts produced in the the fall or during cold damp weather, or the mature plants after a light frost may contain quantities of hydrocyanic acid that are poisonous for livestock. The intravenous injection of sodium nitrite solutions as soon as symptoms of the poisoning are noticed has been found effective as an antidote.

Another naturally occurring glucoside is *indican.* On hydrolysis it yields glucose and indoxyl. Indoxyl is colorless and readily undergoes oxidation on contact with air to give the dye indigo blue. Indican was formerly the source of this important dye, but now it has been supplanted by synthetic products (see page 503).

Other substances that are related in general structure to the glucosides are the digitalis and saponin glycosides. The leaves of the foxglove contain at least five glycosides that are the active principles of digitalis, used in the treatment of heart diseases. The digitalis glycosides decrease the frequency and strengthen the intensity of the heartbeat. No universally satisfactory substitute has been found to replace the digitalis glycosides in medicine.

The saponins are a class of glycosides widely distributed in plants. The characteristic properties of this class of glycosides are the production of a soapy foam on mixing with water and their toxicity to cold-blooded animals, such as fish and frogs. Formerly, they were used to increase the foaming of beverages, such as beer, but since they now are known to have a dissolving action on the red blood corpuscles, this use generally is prohibited by law. The aborigines of South America employed the saponins as fish poisons. The macerated root of plants containing saponins was thrown on the lake or river, and the fish that floated to the surface were collected. The saponins are toxic to fish in concentrations of one part of this glycoside to 1,000,000 parts of water.

Study Questions

1. What is the function of pentosans in plants? What are sources of xylan and araban?
2. What is the function of starch in the plant? Describe the process for the isolation of starch from corn.
3. List four reasons why starch has been studied so extensively.
4. What is the most widely used method of measuring the amount of swelling or hydration of starch? What are some compounds that will cause the gelatinization of starch at room temperature?
5. What are the two principal components of the starch granule? Which of these is present in the greater amount? Describe a method by which the components can be separated from each other.
6. How do α-amylase and β amylase differ in their hydrolyzing action on starch?
7. What are the names of the various dextrins resulting from the action of α-amylase on starch? What color reactions with iodine do these dextrins yield?
8. Of what significance is the isolation of cellotriose from cellulose?
9. Describe the production of corn syrup from cornstarch. What are some uses of this product?
10. How is D-glucose, or dextrose, obtained from starch? What are some uses of this product?
11. List six uses of starch.
12. What is another name for animal starch? In what three particulars does it differ from plant starch?
13. From what sources can inulin be isolated? What sugar does it yield on hydrolysis?
14. What are the functions of cellulose in plants?
15. What is the portion of cellulose that is insoluble in 17.5 per cent sodium hydroxide called? Approximately what percentage of this component is contained in cotton? In wood?
16. What is the name of the disaccharide unit in cellulose? Write the perspective formula for this compound.
17. What is H. Mark's theory in regard to the arrangement of the cellulose molecules in fibers?
18. Describe briefly the three principal methods for the manufacture of rayon. Name the principal chemicals used in each process.
19. In what respect does cellulose acetate differ chemically from the other types of rayon?

20. What are some of the advantages and disadvantages of cellulose acetate as a textile fiber?
21. What is Cel-O-Glass? For what is it used?
22. Describe the manufacture of smokeless powder.
23. What is pyroxylin? What are some uses of this compound? How is celluloid related to pyroxylin?
24. What are some advantages that rayon possesses over the natural fibers? How is spun rayon made? How does it compare in cost with the ordinary type of rayon?
25. Explain how the manufacturers can claim that nylon is made from "coal, air, and water."
26. What are some uses of the large diameter, monofilament nylon?
27. What are the basic chemical substances used in vinyon? What characteristics do vinyon fabrics possess that make them valuable for use as filter cloth for chemical solutions?
28. Why is fabric made from glass fibers not breakable like ordinary glass? What are some practical uses of Fiberglas?
29. Name several textile fibers made from proteins as a raw material.
30. What are two industrial sources of pectin?
31. What are the optimal conditions for jelly making?
32. Name a typical gum and tell for what it is used. What types of product are obtained when gums are boiled with acid?
33. In what respect do mucilages differ from gums? Name a mucilage of commercial importance.
34. What is the name of one process for removing lignin from wood? Upon what chemical transformation in the lignin does this depend?
35. What is the characteristic chemical group that is found in lignin from all sources?
36. Write the type formula for a glucoside. What is the aglucone group in arbutin?
37. What is the principal use of phlorhizin? Of salicin?
38. How do you account for the development of the brilliant autumnal foliage?
39. Why is dhurrin of importance?
40. What is the physiological effect of the digitalis glucosides?

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CHAPTER XVI

AROMATIC HYDROCARBONS

Introduction.—The organic compounds we have discussed thus far have belonged to the large class of substances termed *aliphatic* compounds. The word "aliphatic" is derived from the Greek word meaning fats, and early in the history of chemistry many of the compounds that we have been discussing actually were obtained from fats. From a structural standpoint a more fundamental concept of aliphatic compounds is that they are "open chain" compounds; the carbon atoms in these compounds are not combined to form closed rings or cycles.*

The section of organic chemistry that we are to consider now is designated *aromatic* chemistry. The word "aromatic" originated from the observations of pioneer organic chemists that certain substances with similar chemical and physical properties all possess a pleasant aroma. Examples of such substances are oil of wintergreen, oil of bitter almonds, and vanilla. Much later it was found that these substances contained their carbon atoms united in closed rings, but the name "aromatic" was retained and is applied to the class of organic compounds that characteristically contain six carbon atoms in a closed ring or cycle. In a typical aromatic compound the ring of six carbon atoms contains three double bonds. It is known now that the property of possessing a pleasant aroma is not a characteristic property of aromatic compounds alone, for aliphatic esters, as a rule, have very agreeable odors. Also, there are certain compounds possessing a closed-ring type of structure that are odorless.

The aromatic compounds will be discussed in much the same sequence as were the aliphatic compounds. Accordingly, we shall consider the aromatic hydrocarbons first.

Benzene

Benzene occupies a more important place in aromatic chemistry than does methane in the aliphatic series of compounds. A great many aromatic compounds are derivatives of benzene, and a great many others are related in structure to it.

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*A few derivatives of the aliphatic compounds, such as anhydrides and lactones, are exceptions to this general statement.

Structure of Benzene.—An analysis for the elements and a molecular weight determination have shown that benzene has the molecular formula C_6H_6. The graphic formula for benzene, however, can be proved only on the basis of chemical reactions. If benzene were an aliphatic compound, it would belong to the series having the general formula C_nH_{2n-6}. This would mean that benzene would be highly unsaturated. If we examine some of the properties of benzene, however, we find that it does not react like an unsaturated compound:

1. Benzene does not react with hydrobromic acid under ordinary conditions.
2. Benzene does not decolorize potassium permanganate, which is used in Baeyer's test for the ethylenic type of double bond.
3. Benzene does not react when mixed with bromine.
4. Benzene does not react with nascent hydrogen (an acid plus a metal).

Hence, judged by the criteria for aliphatic compounds, we must conclude that benzene behaves like a saturated compound. On the other hand, if we examine the reactions that benzene undergoes, we find that in the presence of finely divided nickel as a catalyst, benzene adds six hydrogens to yield a compound with the formula C_6H_{12}. *This reaction indicates the presence of three double bonds in benzene.*

$$\underset{\text{Benzene}}{C_6H_6} + 3\,H_2 \xrightarrow{\text{Ni}} \underset{\text{Hexahydrobenzene}}{C_6H_{12}}$$

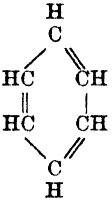
Although benzene does not react when mixed with bromine, substitution takes place if a catalyst such as iron filings is present.

$$\underset{\text{Benzene}}{C_6H_6} + Br_2 \xrightarrow[\text{filings}]{\text{Fe}} \underset{\text{Bromobenzene}}{C_6H_5Br} + HBr$$

Regardless of the conditions or the halogen used, *one and only one* monosubstituted product of benzene can be obtained. This reaction shows that all the hydrogens in benzene are equivalent;

otherwise, more than one monosubstitution product could result from the reaction. A graphic formula for benzene that explains its reactions must take into account the presence of three double bonds and the equivalence of the six hydrogens. The proposal of a formula for benzene that would meet these requirements satisfactorily was one of the most perplexing problems that confronted organic chemists in the middle of the nineteenth century. The formula that has stood most satisfactorily the test of time is the one proposed by Kekulé in 1865. Kekulé, a German chemist, was teaching in London at the time. The story goes that Kekulé was sitting in front of his fireplace one night, dozing and dreaming. In one of his dreams, it is said, he saw a snake bite its tail. This gave him the idea of a ring structure for benzene. Whether or not imbibition of fermented beverages had an effect on the zoological nature of his dream is not reported.

The structural formula for benzene proposed by Kekulé is as follows:

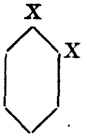


Benzene

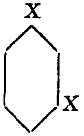
The alternate double bonds account for the unsatisfied valences of carbon and explain the possibility of the addition of six hydrogen atoms. The relationship of each of the carbon atoms to the molecule is the same, so that the hydrogen atoms attached to these carbon atoms are equivalent. This equivalence is reflected in the formation of only one monosubstitution product.

For convenience in printing, the formula of benzene is represented sometimes by a hexagon. The double bonds and the hydrogens are not shown. However, the student should remember continually that there are alternate double bonds, and that a hydrogen atom is attached to each carbon atom unless some other group is indicated, signifying that one of the hydrogens has been replaced.

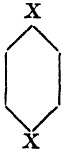
From an examination of the Kekulé formula for benzene, it could be predicted that there would be three disubstitution products of benzene. This has been found to be true. Assuming X to represent a group that has substituted for a hydrogen atom, the structures of the three isomers are:



Ortho (o)



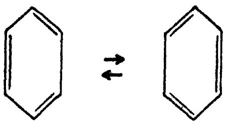
Meta (m)



Para (p)

The isomer in which the substituted groups are on adjacent carbon atoms is termed *ortho,* often abbreviated o-. The isomer having one carbon atom between the two substituted groups is known as *meta* (m-). The third isomer, in which the substituted groups are on the carbons across the ring from each other, or in which there are two carbon atoms intervening, is designated the *para* isomer (p-).

One objection that soon was raised to the formula for benzene proposed by Kekulé centers about its possession of double bonds. From the formula it would seem that there should be two compounds, instead of only one, when the substituted groups are adjacent to each other. It was pointed out that this necessarily would follow, because in one instance the carbons carrying the two substituted groups would be connected by a double bond, while in the other instance the carbons would be linked by a single bond. This objection to the Kekulé formula was met by the hypothesis that the double bonds in the proposed formula are not static, but are shifting continually between two adjacent positions, as the following diagrams illustrate:



The two forms are equivalent and indistinguishable from each other; their interconversion requires only a redistribution of the valence electrons. Such a phenomena is known as *resonance.* It accounts for the relative stability and the lowered reactivity of benzene. X-ray data of crystalline derivatives of benzene show that all the C—C bonds in benzene are of the same length. However, they are slightly longer than the ordinary C—C single bond, but shorter than the space in a regular C=C double bond. This correlates with the idea that benzene is a *resonating hybrid.*

Commercial Source of Benzene.—Benzene is one of the byproducts resulting from the destructive distillation of bituminous (soft) coal. When coal is heated in a closed chamber in the absence of air, the products that are separated from the distillation of one ton of coal are:

	Distillation products from one ton of soft coal
Gases (hydrogen, methane, carbon monoxide)	10,000-11,000 cu. ft.
Ammonium sulfate	18-30 pounds
Coke	1,200-1,500 pounds
Coal tar	10-15 gallons

The gases are used to heat the coke ovens or are sold to municipalities as domestic fuel. The ammonia is separated by passage through sulfuric acid solution in which the ammonia is retained as ammonium sulfate. The coke is used principally in the metallurgical industry for the reduction of ores to the free metals. The coal tar fraction is the principal source of aromatic compounds. In general, the following fractions are separated:

1. Light oil fraction (up to 170° C.)
    - Benzene
    - Toluene
    - Xylene
2. Middle oil (up to 225° C.)
    - Phenol
    - Naphthalene
    - Pyridine bases
3. Creosote oil (heavy oil) (up to 270° C.)
    - Cresols
4. Green oil (up to 320° C.)
    - Anthracene
    - Phenanthrene

Laboratory Preparation of Benzene.—Benzene obtained from coal tar always contains a small amount of thiophene, a sulfur compound that can be removed only by chemical treatment. Pure benzene can be prepared in the laboratory by the polymerization of acetylene in a hot tube. Three molecules of acetylene polymerize to give a molecule of benzene. This reaction illustrates the preparation of an aromatic compound from an unsaturated aliphatic compound.

$$\underset{\text{Acetylene}}{3\,C_2H_2} \xrightarrow[\text{Fe-Si-Cr catalysts}]{650^\circ\text{ C.}} \underset{\text{Benzene}}{C_6H_6}$$

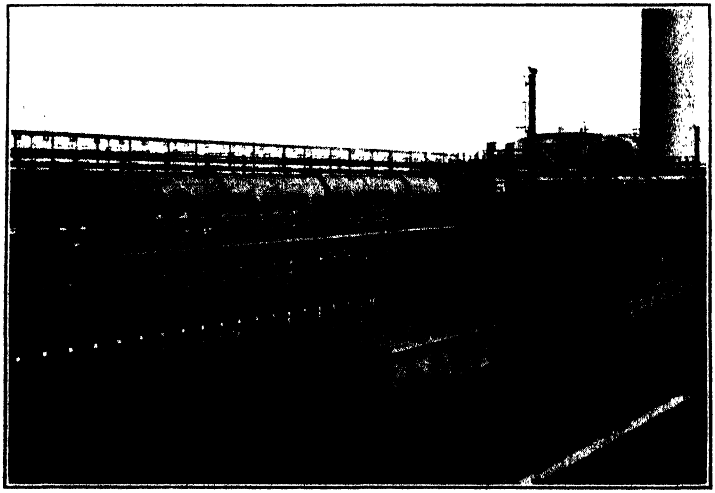


Fig. 57.—Battery of Koppers by-product coke ovens. The large horizontal pipe at the top of the ovens is for the collection of the coal tar and other volatile substances driven off during the coking process. Coal tar obtained by this process is the principal source of aromatic compounds. (Courtesy of Ketchum, Macleod, and Grove, Inc.)

Benzene is a colorless liquid boiling at 80.4° C. It is insoluble in water, but is soluble in alcohol and ether. Benzene is toxic to man. Taken internally, it is fatal. If low concentrations of the vapors are inhaled over a long period of time, a decrease in the production of both the red and white blood corpuscles, which may result in death, takes place. Contact with the skin also is harmful.

Large quantities of benzene are used in motor fuel to increase the antiknock value of the gasoline. The so-called benzol blends are such mixtures. Benzene is used as a solvent for rubber, fats, and resins, and in the preparation of rubber cement. It is the starting material for the manufacture of a large number of other aromatic compounds, such as synthetic phenol, nitrobenzene, aniline, chlorobenzene, and others.

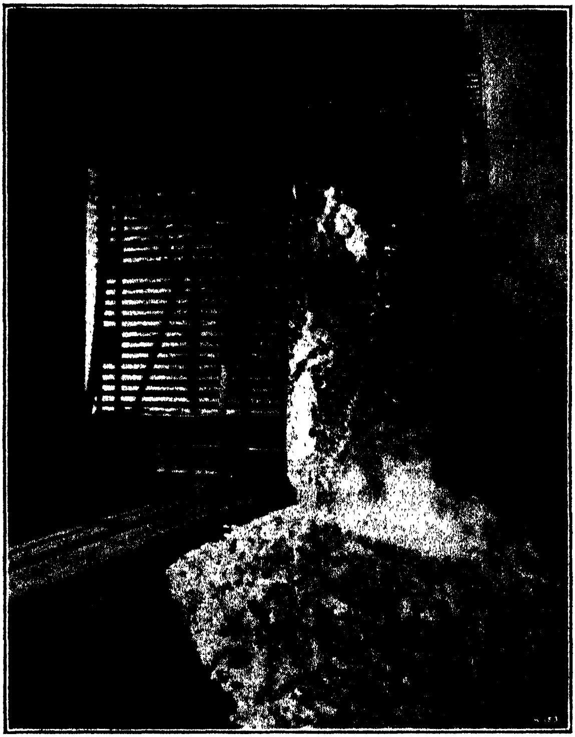
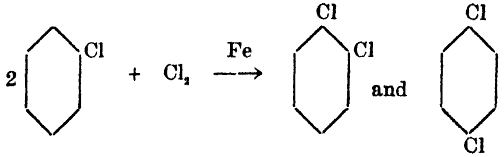


Fig. 58.—Red-hot coke being "pushed" in a single stroke of a ram from a Koppers by-product coke oven into a waiting railroad car after the removal of the volatile products. Coke is a highly strategic material in the manufacture of steel. The demand for coke has become so great that the old-time, beehive type of ovens, which do not recover the by-products, again are being used in order to supply the demand. (Courtesy of Ketchum, Macleod, and Grove, Inc.)

Chemical Properties of Benzene.—Three important substitution reactions of benzene are halogenation, nitration, and sulfonation. These reactions differ from the corresponding ones in the aliphatic series in several important respects. The differences exhibited by these reactions illustrate more than anything else the characteristic properties of aromatic compounds.

Halogenation. Chlorine and bromine can be introduced into the benzene ring by the direct action of the halogens on benzene in the presence of a catalyst. Chlorobenzene is an example of an *aryl halide,* which corresponds to an alkyl halide in the aliphatic series. The aryl halides differ markedly from the alkyl halides in some of their properties. The outstanding difference between the two classes of compounds is the nonreactivity of the halogen atom in the aryl halides. With sodium hydroxide, alkyl halides yield alcohols, but the halogen atom in aryl halides is not replaced by an hydroxyl group when the halide is treated with sodium hydroxide at ordinary temperature and pressure. At high temperature and pressure, however, sodium hydroxide reacts with chlorobenzene to form hydroxybenzene or phenol. Neither does ammonia react with the halogen in aryl halides under ordinary conditions to give amino compounds. At high temperature and pressure reaction occurs, with the formation of amines. The aryl halides, however, react with magnesium to form Grignard reagents, and with sodium to give hydrocarbons of high-molecular weight.

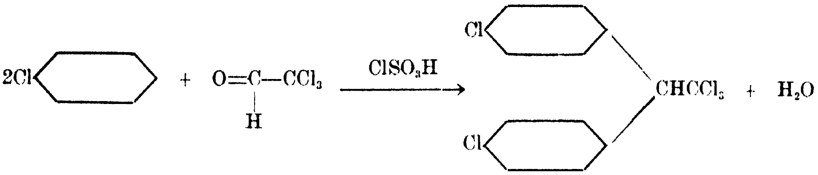
At high temperatures and with a high concentration of halogen, the dihalogen derivatives of benzene can be prepared. When two hydrogens are substituted, there are, as we have learned, three possible isomers; hence, there are three dichlorobenzenes. The product obtained by the further chlorination of chlorobenzene is a mixture of seven parts of para isomer to one part of ortho isomer. Only a small amount of the meta isomer is formed.



Chlorobenzene o-Dichlorobenzene p-Dichlorobenzene

In 1946 the production of p-dichlorobenzene amounted to 31,128,000 pounds. p-Dichlorobenzene is used widely as an insecticide to protect woolens from moths, and to protect peach trees from the peach tree borer.

Chlorobenzene, when it is heated with chloral in the presence of a condensing agent such as chlorosulfonic acid, yields dichlorodiphenyltrichloroethane, or D.D.T., the widely used insecticide.



Chlorobenzene Chloral D.D.T.

In 1946 about 48,000,000 pounds of D.D.T. were produced.

Hexachlorobenzene, Gammexane ($Cl_6C_6H_6$), is the first insecticide that gives promise of destroying the cotton boll weevil. This insecticide is a three-way poison—a contact, a stomach, and a fumigant insecticide. To some insects it is several times as toxic as D.D.T., but it is much less toxic to warm-blooded animals.

Orientation of Substituting Groups in the Benzene Ring. If one of the hydrogens in benzene is substituted by a group or atom, the position taken by a second element or group in the ring does not occur in a haphazard fashion, but takes place in a predictable manner. The position taken by the second group is dependent on the nature of the group already present in the molecule, and is almost independent of the nature of the entering atom or group. With the advent of new knowledge of aromatic structure, and the development of theoretical organic chemistry, an explanation for the selection of the position taken by a particular group now is possible. Such explanations, however, are much too involved for the beginner. The following empirical rules, the essentials of which were proposed by Vorländer in 1902, will suffice for our purpose.

1. If the atom or group *attached* to the benzene ring is saturated (carries only single bonds), the entering group will

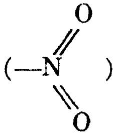
take mainly the position ortho or para to the position of the group already present. Such *ortho* and *para directing* groups are:

- a. The halogens (F, Cl, Br, and I)
- b. The hydroxyl group (—OH)
- c. Alkyl groups (CH_3—, C_2H_5—, etc.)
- d. Substituted alkyl groups (CH_2X—)
- e. Ether groups (—OR)
- f. Primary, secondary, and tertiary amines (NH_2, NHR, NR_2)
- g. Substituted amines (—NHCOR)

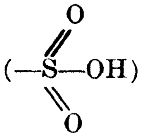
The hydroxyl group has the most powerful influence of the ortho-para directing groups. The directing influence of the ortho-para groups can be listed in order as:

$$\mathrm{OH} > \mathrm{NH_2} > \mathrm{NR_2} > \mathrm{NHR} > \mathrm{Cl} > \mathrm{Br} > \mathrm{Alkyl} > \mathrm{I}$$

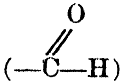
2. If the atom attached to the benzene ring carries a double or triple bond, then the entering atom or group will enter mainly the position meta to the atom or group already present. Examples of *meta directing groups* are:

a. Nitro group 

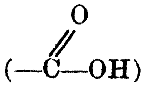
$(-\overset{O}{\underset{O}{N}})$

b. Sulfonic acid group 

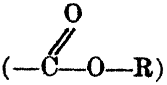
$(-\overset{O}{\underset{O}{S}}-OH)$

c. The aldehyde group 

$(-\overset{O}{C}-H)$

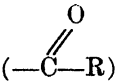
d. The carboxyl group 

$(-\overset{O}{C}-OH)$

e. Ester group 

$(-\overset{O}{C}-O-R)$

f. Ketone group



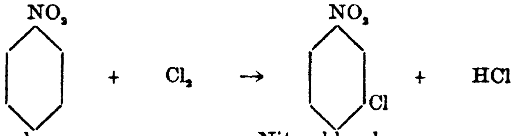
$$(-\overset{\overset{\displaystyle O}{/\!/}}{C}-R)$$

g. Cyanide group ($C\equiv N$)

The carboxyl group is the most powerful of the meta-directing groups. In case of competition between meta directing and ortho-para directing groups, the ortho-para directing group can be expected to take precedence over the meta directing group.

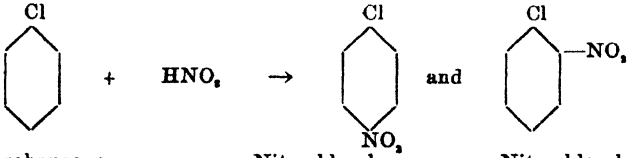
It is essential that the student drill himself until he is thoroughly familiar with the groups that are ortho and para directing, in contrast to those that have a meta directing influence.

If nitrobenzene is chlorinated, the directing influence of the nitro group attached to the ring results in the formation of m-nitrochlorobenzene.



Nitrobenzene m-Nitrochlorobenzene

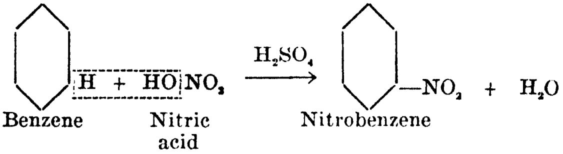
On the other hand, if chlorobenzene is nitrated, a mixture of ortho- and para-nitrochlorobenzene is obtained because of the ortho and para directing influence of the chlorine atom attached to the ring. These reactions illustrate that the nature of the group already present is the all-important factor in determining the position taken by a second entering group.



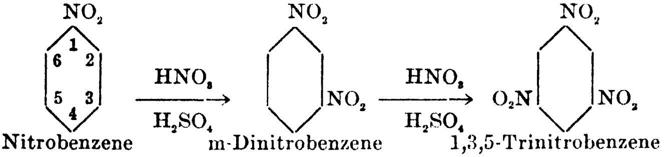
Chlorobenzene p-Nitrochlorobenzene o-Nitrochlorobenzene

The relative amounts of the ortho and para isomers formed depend upon such experimental conditions as temperature, concentration of reacting substances, and catalysts.

Nitration. Benzene and other aromatic hydrocarbons react directly with concentrated nitric acid to form nitro compounds. Under similar conditions, aliphatic compounds undergo oxidation. In practice, *nitration* is carried out by means of a mixture of concentrated nitric and sulfuric acids, the sulfuric acid serving to remove the water formed in the reaction.

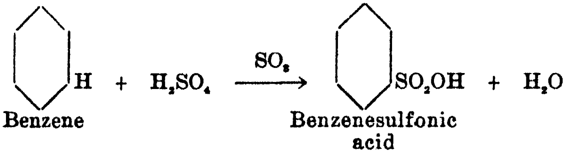


The introduction of a second nitro group into the benzene molecule requires the use of higher concentrations of nitric acid (fuming nitric acid usually is employed) and a higher reaction temperature. A m-dinitro compound is the principal reaction product. A third group enters with still greater difficulty. Not more than three nitro groups can be introduced by direct nitration. The final product of nitration is 1,3,5-trinitrobenzene.

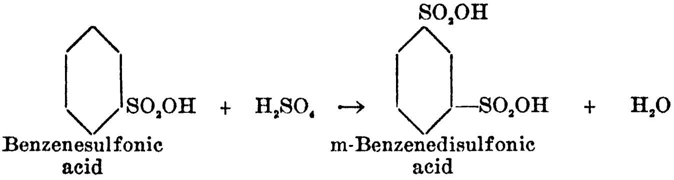


Nitrobenzene ($C_6H_5NO_2$), or oil of mirbane, is a pale, yellow liquid with an odor resembling that of bitter almonds. It is a poisonous compound. Because of its odor, it is used to replace oil of bitter almonds in perfumes, such as are used in soaps. Its chief use, however, is in the preparation of aniline (see page 466).

Sulfonation. Concentrated sulfuric acid containing dissolved sulfur trioxide reacts with the aromatic hydrocarbons to form sulfonic acids. The aliphatic saturated hydrocarbons, in general, are not affected by the action of sulfuric acid. The first product of *sulfonation* is benzenesulfonic acid.



If the reaction is continued, using higher temperature, a disulfonic acid is formed.



The sulfonic acids are strongly acidic in character. The sulfur is attached directly to the carbon, instead of being linked through an oxygen, as in ethyl hydrogen sulfate ($C_2H_5—O—SO_2OH$); thus the sulfonic acids are stable compounds and can be hydrolyzed only with difficulty.

Many sulfonic acids are crystalline solids, very soluble in water. Their barium and calcium salts are also water soluble, in contrast to the insoluble inorganic sulfates. Sulfonic acids and their salts are useful in organic syntheses. Because sulfonic acid salts are more soluble in water than the original compound subjected to sulfonation, many insoluble dyes are made water soluble by the introduction of the $—SO_3H$ group.

Homologues of Benzene

Toluene.—The first higher homologue of benzene is toluene, $C_6H_5CH_3$. Toluene is obtained from the light oil fractions resulting from the high-temperature carbonization of coal. It is produced also from petroleum by the aromatization of n-heptane (see page 90). Toluene is a water-clear liquid resembling benzene in odor. It can be prepared in the laboratory by the reaction of benzene and an alkyl halide in the presence of anhydrous aluminum chloride. This is known as *Friedel-Crafts* reaction. This reaction is much used for the preparation of higher alkylated benzenes.

$$\underset{\text{Benzene}}{C_6H_6} + \underset{\substack{\text{Methyl}\\\text{bromide}}}{CH_3Br} \xrightarrow{\substack{\text{anhydrous}\\AlCl_3}} \underset{\text{Toluene}}{C_6H_5CH_3} + HBr$$

Another laboratory method of preparing toluene is by the *Fittig synthesis,* which utilizes the action of sodium on an aryl and an alkyl halide.

$$\underset{\text{Bromobenzene}}{C_6H_5Br} + \underset{\text{Methyl bromide}}{CH_3Br} + \underset{\text{Sodium}}{2\,Na} \rightarrow \underset{\text{Toluene}}{C_6H_5CH_3} + \underset{\text{Sodium bromide}}{2\,NaBr}$$

This reaction is similar to the Wurtz synthesis for the preparation of aliphatic hydrocarbons (see page 70).

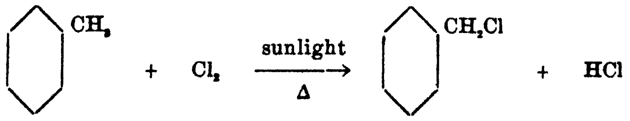
Chemical Properties of Toluene.—The chemical properties of toluene are similar to those of benzene—halogenation, nitration, and sulfonation being the principal types of reaction. The methyl ($—CH_3$) group of toluene is referred to as a side chain, and some of the reactions peculiar to toluene are dependent on the presence of this group.

Oxidation. One of these reactions is oxidation. The action of oxidizing agents on toluene produces benzoic acid, C_6H_5COOH. This type of reaction is general for benzene derivatives containing carbon side chains. On vigorous oxidation the carbon side chain always is oxidized to a carboxyl group regardless of the length of the carbon chain.

$$\underset{\text{Toluene}}{C_6H_5CH_3} \xrightarrow[\text{or } KMnO_4]{K_2Cr_2O_7} \underset{\text{Benzoic acid}}{C_6H_5COOH}$$

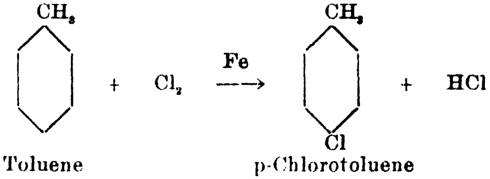
Halogenation. The presence of the methyl group in toluene affords the possibility of differences in halogenation: a halogen atom can substitute for a hydrogen in the ring or for a hydrogen in the side chain.

1. In the presence of sunlight and at the boiling temperature of toluene, substitution takes place in the side chain.



Toluene Benzyl chloride

2. In the presence of certain catalysts (such as iron) halogenation takes place in the ring, as would be the case if the methyl group were not present.

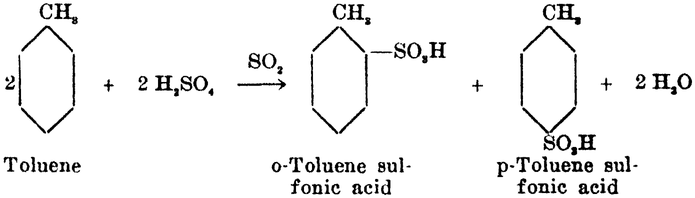


A simple mnemonic device that may be helpful to the student in distinguishing between the two types of halogenation products under the different conditions is:

Sunlight
Side chain

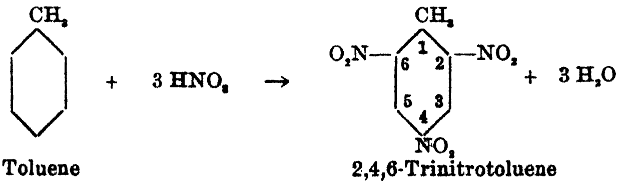
Catalyst
Cyclic substitution

Sulfonation. The sulfonation of toluene is similar to the sulfonation of benzene, the difference being that the presence of the methyl group directs the entering sulfonic acid group to the ortho and para positions.



Toluene sulfonic acids are used in the preparation of dyes and other compounds.

Nitration. The nitration of toluene is presented because of the importance of the trinitrated product.



In naming the derivatives of benzene, it often is found convenient to number the carbon atoms in the cycle from one to six. Trinitrotoluene then can be termed 2,4,6-trinitrotoluene.

The first letters of the three parts of the chemical name form the familiar abbreviation T.N.T. Trinitrotoluene is valued as a military explosive because of its relative stability in comparison with other explosives. It requires a detonator, such as fulminate of mercury, to set off the explosion. Trinitrotoluene is a solid, but it can be melted and poured into shells without danger of explosion during handling. Its melting point is 81° C.

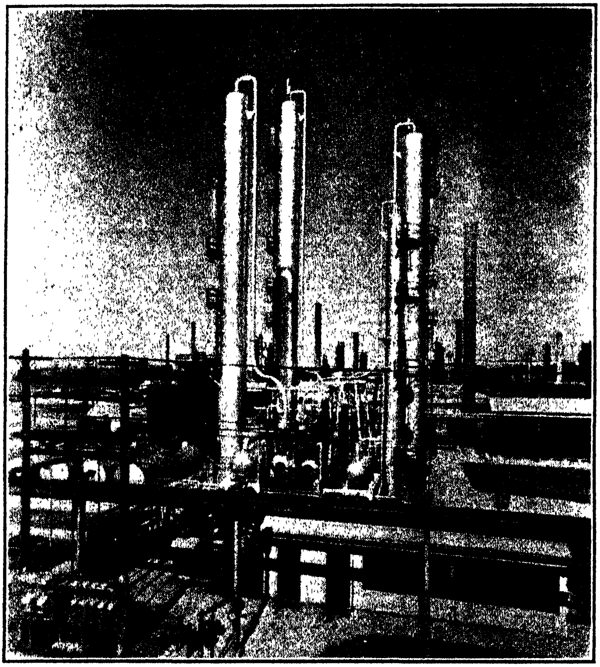
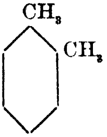


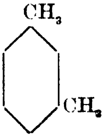
Fig. 59.—A sectional view of the new toluene plant at the refinery of the Shell Oil Company, Houston, Texas. Plants like this one, which used petroleum as a source of toluene, afforded ample supplies of toluene to meet the urgent demands for the manufacture of T.N.T. during World War II. Before the development of this process, the supply of toluene was dependent solely on the amount obtained from coal tar. (Courtesy of the Shell Oil Company.)

In addition to the large quantities of toluene used in the preparation of explosives, toluene is used for the preparation of benzoic acid, benzaldehyde, and dyestuff intermediates. Toluene is a good solvent for resins and lacquers, and before the increased demand of the explosive industry, it was being added to motor fuel to increase its octane rating. During World War I the price of toluene skyrocketed to several dollars a gallon as a result of the inability of the coking industry to supply the demand. This state of affairs is not likely to occur again, since processes for the manufacture of toluene from petroleum have been perfected. In fact, the supply of toluene available from coke oven and petroleum sources is far in excess of all industrial requirements.

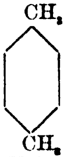
Xylene.—The second higher homologue of benzene contains two methyl groups, and is known as xylene. As is true for all disubstitution products of benzene, there are three isomers: ortho, para, and meta xylenes.



o-Xylene



m-Xylene

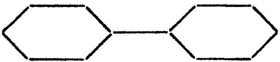


p-Xylene

Xylenes are obtained from the light oil fraction of coal tar. Their chemical properties do not differ much from those of toluene. They are employed as solvents for resins and lacquers, and also are used in the preparation of compounds for the synthesis of dyes.

Diphenyl

Diphenyl, or biphenyl, is a compound made by passing benzene vapors over a heated catalyst. One hydrogen atom is lost from each benzene molecule when diphenyl is formed.

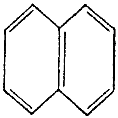


Diphenyl

Diphenyl reacts like benzene in many instances. It can be chlorinated, nitrated, and sulfonated. However, the student should note that it is *not* a homologue of benzene. It contains two benzene rings linked by a single bond. The name of the compound is derived from the fact that the benzene ring minus one hydrogen atom, C_6H_5, is known as the phenyl radical, hence diphenyl. The phenyl radical bears the same relationship to benzene as the methyl radical bears to methane. The chief use of diphenyl is as a heat transfer agent. Since it is a relatively stable compound with a high boiling point, boilers in which it is used can operate at high temperatures and at relatively low pressures.

Naphthalene

Another aromatic compound containing two benzene rings is naphthalene. In this case, however, the rings are attached to each other at the points of two carbon atoms. Naphthalene is the simplest aromatic hydrocarbon with *condensed* or "fused" benzene rings, two carbons being common to each benzene ring.



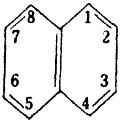
Naphthalene

Naphthalene is obtained from the middle oil fraction of the coking process. It distills at about 217° C. About 30 pounds of naphthalene are obtained from the distillation of one ton of coal. Larger amounts of naphthalene than of any other single hydrocarbon are obtained from the coking process.

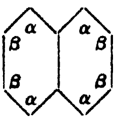
Crude naphthalene is a light gray to tan colored, granular solid that has a tarlike odor, caused by traces of impurities of tar oils that distill in the same range as does the naphthalene. It is used in the manufacture of phthalic anhydride (see page 463), in the dyestuff industry, and in making synthetic resins for plastics. It is used also in the manufacture of dry dips for stock and cattle bedding, and in various powdered insecticides.

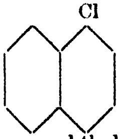
Naphthalene is purified by sublimation (a process of passing from the solid to the gaseous state without going through the liquid stage). Purified naphthalene is a white solid familiar to everyone in the form of "moth balls." A number of forms of purified naphthalene are marketed in order to suit the particular needs of the consumers; for example, there are crushed, flake, and ball forms of naphthalene. Chemically, these products are identical; they differ only in the mechanical treatment of the original material. The largest consumer of refined naphthalene is the chemical industry. The compound can be sulfonated, chlorinated, halogenated, and oxidized. The derivatives are important chemicals in the dye industry, and are important also as organic solvents and as insecticides. Large quantities of naphthalene are used in the destruction of clothes moths. As is commonly known, naphthalene sublimes even at ordinary temperatures. It is one of the oldest, least expensive, and most effective materials for controlling moths. One pound should be used for each 50 to 100 cubic feet of tightly closed space.

In naming the derivatives of naphthalene, the substituted groups are given a number according to their position on the rings. There are eight replaceable hydrogen atoms in the naphthalene molecule.

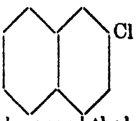


The molecule is symmetrical in its structure, so that positions 1,4,5, and 8 are identical (α), as are positions 2,3,6, and 7 (β). Thus, in reality, there are two possible monosubstitution products of naphthalene; they are known as the *alpha* and *beta* forms.





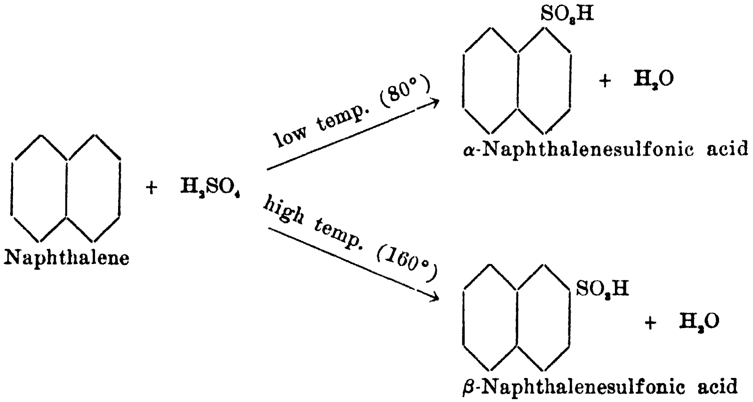
α-Chloronaphthalene



β-Chloronaphthalene

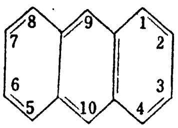
Naphthalene undergoes the reactions typical of aromatic hydrocarbons—direct halogenation and nitration to yield chiefly the alpha derivatives. In the formation of naphthalenesulfonic acids, at about 80° C., the main product is α-sulfonic acid; at 160° C. or higher, the β-sulfonic acid predominates.

The naphthalenesulfonic acids are used widely, owing to the ease with which the sulfonic group can be replaced by such groups as the hydroxyl or the amino. In fact, in the aromatic series the sulfonic acids are as useful in organic syntheses as the aliphatic halides are among aliphatic compounds.



Anthracene

Anthracene is present in the coal tar fraction that boils above 270° C. It is more difficult to isolate and to purify than are the other coal tar crudes. It forms colorless plates that exhibit a blue fluorescence. The anthracene nucleus is numbered in the same manner as naphthalene to facilitate the naming of derivatives.

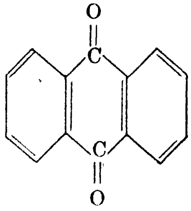


Anthracene

An outstanding characteristic of athracene is the reactivity of the two carbon atoms in the middle ring. When anthracene is oxidized with chromic acid and sulfuric acid, anthraquinone is obtained.

Nitric acid, when it reacts with anthracene, does not give rise to nitro derivatives, as has been the case in the other aromatic hydrocarbons discussed thus far; instead, anthraquinone is formed. This indicates that the two central carbon atoms (9 and

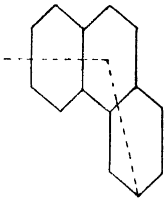
10) of anthracene differ somewhat from the carbons in the two outside rings. Anthracene and anthraquinone are important products in the manufacture of dyes and dye intermediates.



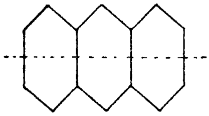
Anthraquinone

Phenanthrene

Another hydrocarbon that contains a condensed nucleus and occurs in coal tar is phenanthrene. Some of its derivatives are physiologically important compounds, since the phenanthrene nucleus is found in the sex hormones, bile acids, sterols, and in a number of carcinogenic compounds (compounds that produce cancerous growths).



Phenanthrene



Anthracene

The union of the rings in phenanthrene is said to be angular, in contrast to the straight-line configuration of anthracene.

Study Questions

1. How do aromatic compounds differ in structure from aliphatic compounds?
2. What is the name and structural formula for the simplest aromatic hydrocarbon? Give the chemical evidence for such a structure.
3. What are the names and formulas for the three possible disubstitution products of benzene, using X to represent a substituted group?
4. Make an outline of the products obtained by the distillation of coal.
5. What are three or four uses of benzene?

6. What is an aryl halide? How do aryl halides differ from alkyl halides?
7. Write the structural formula for p-dichlorobenzene. What is a use of this product?
8. State the rules for substitution in the benzene ring and give examples illustrating the operation of these rules.
9. Write an equation to illustrate the progressive nitration of benzene, naming all the compounds involved.
10. How do sulfonic acids differ from sulfate compounds? Write formulas of typical examples to illustrate your answer.
11. What is the catalyst in the Friedel-Crafts reaction, and what type of compounds can be prepared by this reaction?
12. What is the name of the first higher homologue of benzene, and from what source is this compound obtained?
13. What compound results upon the oxidation of benzene derivatives containing carbon side chains?
14. Toluene on halogenation gives what two types of derivatives? What conditions determine which type of derivative is formed in a given reaction?
15. What nitrated product of toluene is a valuable explosive?
16. What is the name of the second higher homologue of benzene? For what is this product used?
17. Why is diphenyl not considered as a homologue of benzene? What is the structural formula of this compound?
18. How do diphenyl and naphthalene differ in structure? What is the commercial source of naphthalene? List several uses of this product.
19. Write the formula for a hypothetical compound, 1-bromo-3-methyl-5-propyl benzene.
20. What is the product obtained upon the oxidation of anthracene?
21. How does the nucleus in phenanthrene differ from the anthracene nucleus?

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CHAPTER XVII

OXYGEN DERIVATIVES OF THE AROMATIC HYDROCARBONS

Introduction.—Aromatic compounds have oxygen derivatives corresponding to the aliphatic oxygen compounds. Thus, there are aromatic alcohols, aldehydes, ketones, and acids. When the functional group of these derivatives is present in the side chain attached to the benzene ring, the compound behaves very much as does the corresponding aliphatic compound. This comparison also holds for other substitution groups present in side chains. For example, the chlorine atom in benzyl chloride, $C_6H_5CH_2Cl$, reacts in a manner similar to that of the chlorine atom in the halide, CH_3CH_2Cl.

Aromatic Alcohols

Benzyl Alcohol, $C_6H_5CH_2OH$.—The simplest aromatic alcohol, benzyl alcohol, occurs free in Peru and Tolu balsams, and as an ester in jasmine, hyacinth, and other essential oils. Benzyl alcohol can be prepared by boiling benzyl chloride with a solution of potassium carbonate.

$$\underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} + HOH \xrightarrow{K_2CO_3} \underset{\text{Benzyl alcohol}}{C_6H_5CH_2OH} + HCl$$

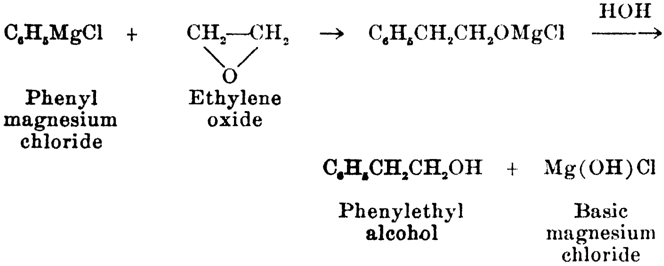
Another means of preparing this aromatic alcohol is by the action of strong alkali on benzaldehyde. This is the *Cannizzaro reaction,* in which there is a simultaneous oxidation and reduction. One molecule of benzaldehyde is oxidized to benzoic acid, and the other is reduced to benzyl alcohol. This type of reaction is characteristic also of formaldehyde.

$$2\,\underset{\text{Benzaldehyde}}{C_6H_5CHO} + NaOH \rightarrow \underset{\substack{\text{Sodium}\\\text{benzoate}}}{C_6H_5COONa} + \underset{\substack{\text{Benzyl}\\\text{alcohol}}}{C_6H_5CH_2OH}$$

Benzyl alcohol is a liquid that is useful in perfumery due to its pleasant odor. The chemical properties of benzyl alcohol are similar to those of the aliphatic alcohols. For example, on oxidation the aldehyde first is formed; further oxidation yields the acid.

$$\underset{\text{Benzyl alcohol}}{C_6H_5CH_2OH} \xrightarrow{\text{Oxidation}} \underset{\text{Benzaldehyde}}{C_6H_5CHO} \xrightarrow{\text{Oxidation}} \underset{\text{Benzoic acid}}{C_6H_5COOH}$$

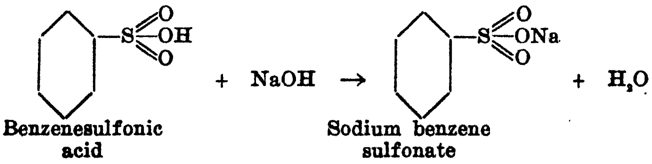
Phenylethyl Alcohol, $C_6H_5CH_2CH_2OH$.—The next higher homologue of benzyl alcohol is phenylethyl alcohol. It occurs in attar of roses, and is used in making perfumes. It can be prepared by the reaction between phenyl magnesium chloride and ethylene oxide.

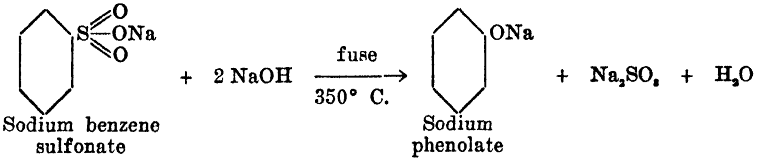


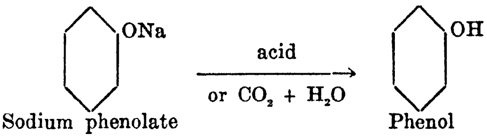
Monohydric Phenols

The aromatic oxygen derivatives in which the hydroxyl group is attached directly to the benzene ring are termed *phenols*. The properties of the phenols differ greatly from those of the aliphatic alcohols. The hydroxyl group in phenols is much more acidic than the hydroxyl group in aliphatic alcohols. The phenols dissolve in dilute sodium hydroxide, whereas the aliphatic alcohols are no more soluble in alkaline solutions than they are in water.

Phenol, C_6H_5OH.—Phenol, or hydroxybenzene, is obtained from the light oil fraction of coal tar. An industrial method for the preparation of phenol is by the fusion of the sodium salt of benzene sulfonic acid with alkali.







Phenol is made also by heating chlorobenzene at 350° C. (using 3,000 pounds pressure) with sodium hydroxide and a copper catalyst. The necessity for these extreme conditions illustrates the nonreactivity of the aryl halides.

$$\underset{\text{Chlorobenzene}}{C_6H_5Cl} + 2\,NaOH \xrightarrow[\text{Cu catalyst}]{\text{350° C., 3,000 lbs. pressure}} \underset{\text{Sodium phenolate}}{C_6H_5ONa} + NaCl + H_2O$$

The sodium phenolate is acidified to liberate phenol.

A recent method for the production of a very pure grade of phenol depends on a catalytic vapor phase reaction for the chlorination of benzene and the hydrolysis of the resulting chlorobenzene. In this process the conversion of benzene to phenol is carried out in two stages. In the first stage, benzene is chlorinated by means of hydrochloric acid and air in the presence of a catalyst. The reaction is exothermic (liberates heat) and proceeds at about 230° C.

$$2\,C_6H_6 + 2\,HCl + O_2 \xrightarrow[\text{catalyst}]{\text{230° C.}} 2\,C_6H_5Cl + 2\,H_2O$$

The second step proceeds at 425° C. and also is carried out in the presence of a catalyst.

$$C_6H_5Cl + H_2O \xrightarrow[\text{catalyst}]{\text{425° C.}} C_6H_5OH + HCl$$

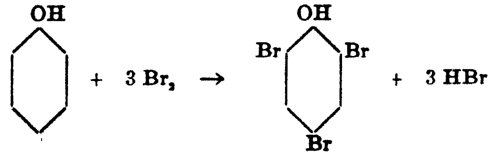
The advantage of this method is that only one-tenth pound of by-products is formed per pound of phenol produced. Other processes previously employed are reported to yield from 2 to 3 pounds of by-products per pound of phenol. Another advantage of this method is that the catalyst in the first stage of the reaction is selective for benzene. Toluene and unsaturated compounds are not chlorinated, but are oxidized to carbon dioxide and water.

Physical Properties.—Pure phenol is a white solid, melting at 41° C. On exposure to air and light it develops a red color. The presence of a small amount of water causes phenol to liquefy. The liquid form more often is termed *carbolic acid* than phenol. Carbolic acid is a poison when it is taken internally, and, if it comes in contact with the skin, its corrosive properties cause blisters. The solubility of phenol in water depends on the temperature of the water. At room temperature it is soluble only to the extent of about 8 per cent, but above 68° C. (154° F.) it is soluble in all proportions. Also, it is soluble in alcohol and ether. This is a fact to be remembered; for if phenol is spilled on the skin, it should be washed off, not with water, but rather with an organic solvent, such as rubbing alcohol.

Chemical Properties.—Phenol is more acidic than are the aliphatic alcohols. This is shown by the fact that it dissolves in dilute solutions of sodium hydroxide, potassium hydroxide, and ammonium hydroxide.

$$\underset{\text{Phenol}}{C_6H_5OH} + NaOH \rightarrow \underset{\substack{\text{Sodium}\\ \text{phenolate}}}{C_6H_5ONa} + H_2O$$

After the substitution of one of the hydrogen atoms of benzene with an hydroxyl group, further substitution is easier. This reactivity is illustrated by the fact that when bromine water is added to a solution of phenol, a white precipitate is formed at once. Upon treatment of this unstable compound, tribromophenolbromide ($Br_4C_6H_2O$), with sodium bisulfite solution, pale yellow crystals of 2,4,6-tribromophenol are formed. The formation of this compound, M.P., 96° C., is used to prove the presence of phenol in an unknown sample.



Phenol

2,4,6-Tribromophenol

One of the halogenated phenols, pentachlorophenol, is sold under the trade name, "Santophen 20." Pentachlorophenol is used to protect wood against degrading agents, such as termites and decay. It has been found to be useful in preserving fence posts from decay; hence less durable woods may be used for this purpose. This preservative is free of objectionable color and odor, and can be applied to wood without altering materially the characteristic appearance, and without affecting subsequent finishing with paints and other coverings. In these respects, it is superior to creosote, a preservative used for treating railroad ties, pilings, and other wooden structures where the appearance of the wood is not an essential factor. The sodium salt, sodium pentachlorophenolate, is claimed to be useful for the preservation of fiber board and cellulosic insulating materials.

Phenol gives a violet color when a few drops of a 5 per cent solution of ferric chloride are added to a few cubic centimeters of it. The color is due to the formation of a negative ion (anion).

$$\underset{\text{Ferric chloride}}{FeCl_3} + \underset{\text{Phenol}}{6\,C_6H_5OH} \rightarrow \underset{\text{Colored ion}}{Fe(OC_6H_5)_6^{---}} + 3\,HCl + 3\,H^+$$

Other compounds containing a phenolic hydroxide group give blue, green, violet, and red colors with ferric chloride. The color formed by phenol and ferric chloride, although it is not specific, is useful in testing for the presence of a phenolic group.

Reduction. Phenol is reduced to the corresponding hydrocarbon when it is distilled at high temperature with zinc dust.

$$\underset{\text{Phenol}}{C_6H_5OH} + Zn \xrightarrow{\Delta} \underset{\text{Benzene}}{C_6H_6} + ZnO$$

Formation of Ethers. Sodium phenolate reacts with alkyl halides to give mixed aromatic-aliphatic ethers. The ether formed with methyl iodide is known as *anisole*. It is a solid with a pleasant odor, and is used in the manufacture of perfumes.

$$\underset{\text{Phenol}}{C_6H_5ONa} + \underset{\text{Methyl iodide}}{ICH_3} \rightarrow \underset{\substack{\text{Methylphenyl ether}\\\text{(anisole)}}}{C_6H_5OCH_3} + NaI$$

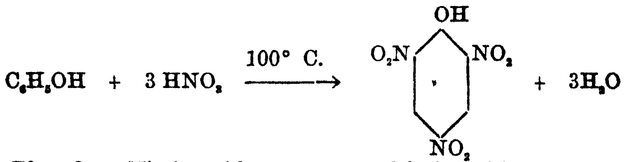
A similar reaction, the *Williamson synthesis,* is used for the preparation of mixed aliphatic ethers. Phenylethyl ether, prepared from sodium phenolate and ethyl iodide, is known as phenetol. It is used in perfumery.

Diphenyl ether, the simplest wholly aromatic ether, is prepared by heating phenol in the presence of zinc chloride. It also is obtained in the manufacture of phenol from chlorobenzene. Diphenyl ether is a solid at ordinary temperatures. It is used in soaps because of its agreeable geranium-like odor and its stability toward alkali.

$$\underset{\text{Phenol}}{2\,C_6H_5OH} \xrightarrow[\Delta]{ZnCl_2} \underset{\text{Diphenyl ether}}{C_6H_5{-}O{-}C_6H_5} + H_2O$$

Diphenyl ether is unaffected by hydriodic acid, which reacts with most ethers to give alkyl or aryl iodides. Due to its inertness toward chemical reagents, and its stability at high temperatures, diphenyl ether is used industrially as a liquid for heat transfer. It is distributed by the Dow Chemical Company under the trade name Dowtherm.

Reaction With Nitric Acid. Reference already has been made to the fact that the substitution of one of the hydrogens of benzene by an hydroxyl group causes the other hydrogens to be replaced more easily by other groups. In order to nitrate benzene, it is necessary to reflux it with concentrated nitric acid in the presence of some sulfuric acid. If one of the hydrogens of benzene is replaced by an hydroxyl to form phenol, nitration takes place with dilute nitric acid at ordinary temperature to yield a mixture of ortho- and para-nitrophenol. If phenol is heated to 100° C. with nitric acid, 2,4,6-trinitrophenol is formed. This compound is known commonly as picric acid.



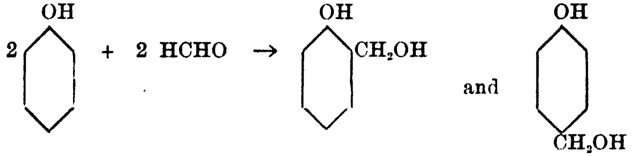
Phenol **Nitric acid** **Picric acid**

Picric acid dyes wool and silk a bright yellow. Formerly, it was widely used, but now it is employed only in conjunction with other dyes to give particular shades. Picric acid is explosive if it is detonated. Since the ammonium salt is more sensitive to detonation, it is the form usually employed in explosives. Picric acid is effective in the treatment of burns, both in the form of a saturated aqueous solution and in a combined form in salves. Butesin picrate, a salve effective as a treatment for burns, is a combination of butesin, a local anesthetic, and picric acid. The local anesthetic relieves the pain of the burn, and picric acid precipitates the protein decomposition products and prevents their being absorbed by the body.

Fig. 60.—Lithcote, a special lacquer with a base of phenolic-formaldehyde resin, is used to line the interiors of this fleet of wine tanks. The surface is smooth, glasslike, nonporous, durable, and will not chip nor crack from the foundation metal. About 376,000 gallons of wine can be transported in this fleet of 47 wine tanks cars. (Courtesy of the Bakelite Corporation.)

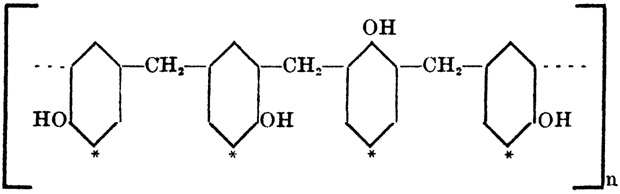
Picric acid forms an insoluble salt with the alkaloids. It often is used in their identification. Another use is as a protein precipitant in separating proteins from solutions. A method for the determination of glucose in blood is dependent on the color formed with picric acid.

Reaction with Formaldehyde, Phenolic Resins, and Plastics. When phenol is heated with formaldehyde either in the presence of a base such as ammonia, or an acid such as sulfuric, the first products formed are hydroxy benzyl alcohols.



Phenol Formaldehyde o-Hydroxy benzyl alcohol p-Hydroxy benzyl alcohol

Upon further heating, these alcohols condense with the elimination of water to form long chain molecules or linear polymers, a portion of which can be represented as having the following probable structure:



Depending on the original phenol-formaldehyde ratio or upon the further action of additional formaldehyde, reactive CH_2OH groups may be present in the positions marked with an asterisk.

If the various conditions such as temperature, time, and amount of formaldehyde are controlled so that relatively low molecular weight products result, *phenolic resins* are formed that can be used for quick-drying enamels and varnishes. These phenolic-formaldehyde resins can be dissolved in solvents to form lacquers. Such resinoid coatings can be baked on products to form a hard, tough surface that is resistant to water, perspiration, some chemical solvents, and which, at the same time provides electrical insulation. Such objects as door handles, belt buckles, vanity cases, textile spinning spools, armatures, and even such large surfaces as the interiors of tank cars and large food processing equipment can be coated with this glossy material. Fig. 60 shows a fleet of 8,000 gallon capacity wine tanks that have lacquer-coated interiors.

Phenolic plastics are formed by the same general type of reaction as the phenolic resins, except that the reaction is carried further and the resulting compounds are of a more complex nature with a higher molecular weight. Upon the addition of more formaldehyde with the proper catalyst, further polymerization occurs and the formaldehyde combines with the resin at the asterisk points in the formula on page 436 to form three-dimensional stable structures. This three-dimensional structure of the polymer is a characteristic of all *thermosetting* plastics; that is, these products become hard and firm upon application of heat. Once the three-dimensional structure has been formed, the thermosetting type of plastic does not soften appreciably on the application of subsequent heat and pressure. Such polymers are valuable plastics since they are stable in form, have high impact strength, are noninflammable, are resistant to high temperature, and are unreactive toward most organic reagents.

The commercial development of phenolics was due to the experiments and enterprise of Baekeland. In 1907 he noted the reaction between phenols and aldehydes; upon the addition of a catalyst and further heat treatment, the resin became hard and could be molded by applying heat and pressure. He realized the commercial possibilities of the product and patented the product, which he called Bakelite. Until his patent expired in 1926, the Bakelite Company was the sole producer of this type of plastic. Since then other companies have put similar products on the market under their own trade names, such as Durite, Resinox, and Texolite.

In general, the phenolic plastics are of two fundamental types—those made by the ''one-stage'' process and those made by the ''two-stage'' process. The one-stage process is used for *cast phenolics*. As the name implies, all the reactants are heated together with a basic catalyst (such as barium hydroxide or caustic soda), are poured into a hot mold, and are further heated until they are hardened or cured. Cast phenolics are available in all colors, both opaque and transparent. They are used for such articles as jewelry, novelties, instrument dials, and interior lighting fixtures.

The two-stage process is used for *molded phenolics.* An acid catalyst is employed in the first step of the reaction which yields a thermoplastic resin. This product is cooled and crushed to form the basic molding powder for the second step of the reaction. In this part of the process more formaldehyde is added with a basic catalyst, along with other ingredients like fillers, pigments and dyes, and mold lubricants. The ingredients are heated in a mold under pressure to form the thermosetting type of plastic. Molded phenolics, unlike the cast products, are available only in the dark colors. In order to obtain even a medium shade, opaque white pigments have to be added to the plastic. These colored phenolics show a lack of stability toward light.

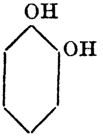
Fig. 61.—Henry Ford's first all plastic automobile body made from molded panels of phenolic-formaldehyde resins with a cellulose filler. The plastic panels in this body design have an impact strength ten times that of steel. (Courtesy of Ford Motor Company.)

Uses of Phenol.—Large quantities of phenol are employed in the manufacture of dyes, drugs (such as aspirin), photographic developers, and plastics. A 3 per cent solution of phenol is an effective disinfectant for inanimate objects, such as surgeons' instruments, containers, and the like. Phenol is not a satisfactory disinfectant for substances containing high percentages of protein material. For example, it reacts to form a hard coagulated mass around pathogenic organisms; there is the possibility, therefore, that the organisms are not destroyed by the action of phenol, but are, instead, only temporarily inactivated.

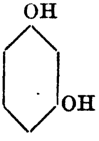
Phenol is used in the refining of lubricating oils since the undesirable aromatic and naphthenic compounds are selectively dissolved, leaving the paraffinic components, which have better lubricating properties.

Dihydroxyphenols

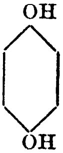
The ortho-, meta-, and para-dihydroxyphenols have specific names.



Pyrocatechol

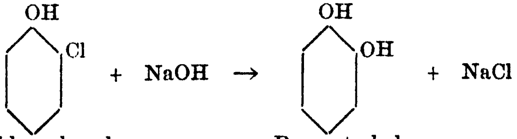


Resorcinol



Hydroquinol

Pyrocatechol.—Pyrocatechol (or catechol) is the ortho-dihydroxybenzene. It was obtained first by heating catechu (a resin obtained from the acacia tree), from which it derives its name. It occurs also in raw beet sugar. Pyrocatechol is prepared commercially by the fusion of o-chlorophenol with sodium hydroxide.

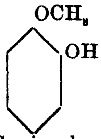


o-Chlorophenol Pyrocatechol

This reaction is an illustration of the effect the hydroxy group has on other substituents in the ring. The chlorine atom in chlorobenzene cannot be replaced by NaOH except under conditions of high temperature and pressure.

Pyrocatechol is much more reactive than benzene. It reduces cold ammoniacal silver solutions and Fehling's solution at the boiling temperature. Due to the ability of this dihydroxyphenol to reduce silver compounds, it is used as a photographic developer. Pyrocatechol also is employed in the manufacture of adrenaline and vanillin.

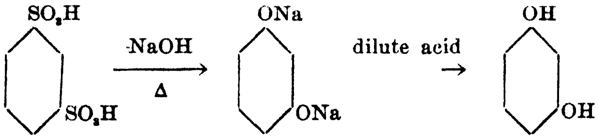
The monomethyl ether of pyrocatechol is obtained as a distillation product of gum guaiacum.



Guaiacol

Guaiacol is used in medicine for the symptomatic treatment of certain inflammations of the respiratory passages. With ferric chloride, guaiacol gives a blue color. Guaiacol in the form of gum guaiacum sometimes is added to lard to retard the onset of rancidity (see page 273).

Resorcinol, m-Dihydroxybenzene.—A frequently used method of preparing resorcinol is by the alkali fusion of m-benzenedisulfonic acid.

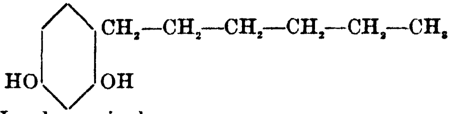


m-Benzenedisulfonic acid

Resorcinol

Resorcinol is a solid that is soluble in water, alcohol, and ether. It acts as a reducing agent in alkaline solutions, but it is not as powerful a reducing agent as pyrocatechol. Metallic silver is formed from ammoniacal silver solutions only on warming. The principal use of resorcinol is in the preparation of dyes. If alcohol, sulfuric acid, and a solution of resorcinol are added to a sugar solution containing a ketose, an intense red color develops. This is known as Seliwanoff's test for the presence of ketoses, especially fructose.

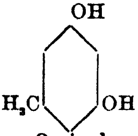
Investigations of the alkyl derivatives of resorcinol showed that the six-carbon derivative had the greatest antiseptic power.



Hexylresorcinol

Hexylresorcinol (Caprokol) is used as an antiseptic. It has been found effective in ridding the intestinal tract of worms. Hexylresorcinol has about 50 times the antiseptic power of phenol.

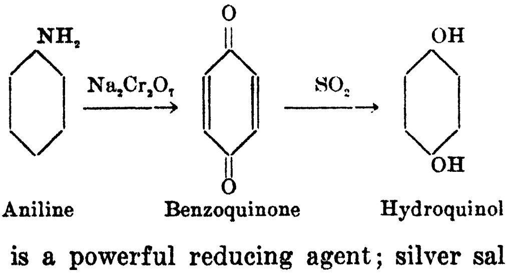
A homologue of resorcinol is orcinol.



Orcinol

This compound is related in structure to the dyes in litmus paper. The reaction of xylose and arabinose in acid solution with orcinol gives characteristic colors. This is Bial's test for the identification of these sugars.

Hydroquinol.—Hydroquinol sometimes is known as quinol, hydroquinone, or p-dihydroxybenzene. This dihydroxybenzene is found in the natural glucoside, *arbutin*, which is present in the bark and roots of pear trees. Hydroquinol is prepared by the oxidation of aniline with sodium dichromate and sulfuric acid. The benzoquinone formed is then reduced with sulfur dioxide.

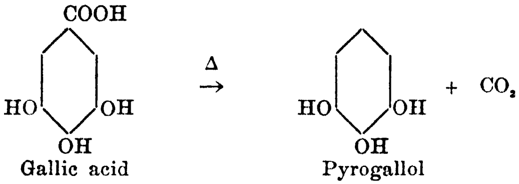


Aniline Benzoquinone Hydroquinol

Hydroquinol is a powerful reducing agent; silver salts are reduced at ordinary temperatures. It is used widely in photographic developers.

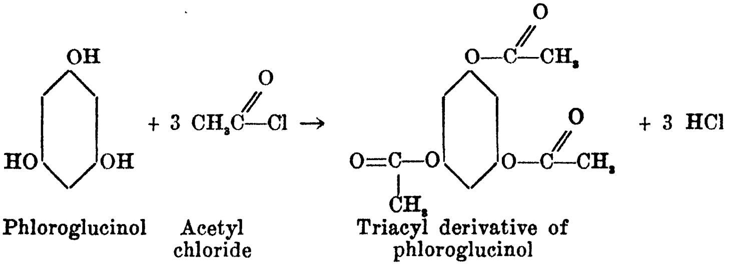
Trihydroxyphenols

Pyrogallol.—Pyrogallol, or 1,2,3-trihydroxybenzene, is obtained by heating gallic acid, secured from the tannins that occur in Chinese nutgalls.

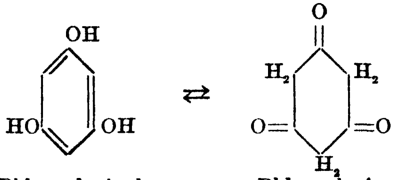


Pyrogallol is a solid that melts at 134° C.; it is soluble in water, alcohol, and ether. It reduces solutions of silver. A characteristic property of pyrogallol is the rapidity with which its alkaline solution absorbs oxygen. Pyrogallol often is utilized in the quantitative absorption of oxygen from a gaseous mixture.

Phloroglucinol.—Phloroglucinol, or 1,3,5-trihydroxybenzene, is a constituent of the glucoside phlorhizin. This glucoside is found in the bark, and particularly the root bark, of apple, pear, cherry, and plum trees. Phloroglucinol has a sweet taste. Only one solid form of phloroglucinol is known, but reactions indicate that there are two forms. With acetyl chloride, a triacetyl derivative is formed.



This indicates the presence of three hydroxyl groups. On the other hand, with hydroxylamine, a reagent used in testing for the carbonyl group in aldehydes and ketones, phloroglucinol forms a trioxime. Accordingly, we can assume that phloroglucinol exists in two forms that are interconvertible. This is an-



Phloroglucinol
Enol form

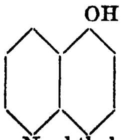
Phloroglucinol
Keto form

other example of tautomerism, such as was encountered in connection with acetoacetic ester. The equilibrium between the two forms is illustrated above.

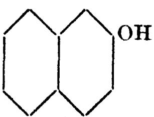
Phloroglucinol, in common with practically all the polyhydroxyphenols, is easily oxidized. Upon this property depends its use as a component of some photographic developers. Phloroglucinol is employed in testing for the presence of pentoses. Arabinose and xylose in acid solution yield a red color with phloroglucinol. On heating, a purplish to black precipitate is produced. One method for the quantitative determination of pentosans is based on the formation of an insoluble phloroglucide with furfural. Pentosans, when heated with 12 per cent hydrochloric acid, yield furfural. This furfural is precipitated with phloroglucinol, and the precipitate is weighed.

Naphthols

The monohydroxy derivatives of naphthalene are known as naphthols. There are two isomeric naphthols; they differ in the position of the hydroxyl group.



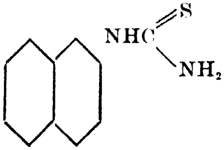
α-Naphthol



β-Naphthol

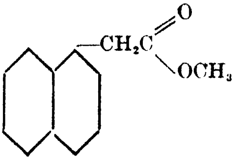
The naphthols can be prepared from the corresponding sulfonic acid derivatives in a manner similar to the preparation of phenol. α-Naphthol is almost insoluble in water, but it is soluble in organic solvents. A test (Molisch) for the presence of carbohydrate in protein material involves the use of α-naphthol. A small amount of a 10 per cent solution of α-naphthol in alcohol is added to a protein solution, and concentrated sulfuric acid is run carefully down the side of a test tube so as to form a layer beneath the lighter aqueous solution. If carbohydrates are present, a reddish-purple ring forms at the zone of contact between the acid and the protein solution.

α-Naphthylthiourea (ANTU), developed during World War II, although not toxic to man, is a potent poison for rats. It is estimated that one pound will kill 300,000 rats.



α-Naphthylthiourea (ANTU)

Another derivative of α-naphthol that is of commercial importance is methyl α-naphthyl acetate. Sprouting of potato tubers stored at 54.5° F. was inhibited by this chemical when it was used on shredded paper in the ratio of 100 mg. to 1 kg. of tubers.



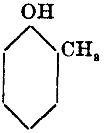
Methyl α-naphthyl acetate

β-Naphthol, which is more soluble than α-naphthol in water, is used in the preparation of a large number of dyes.

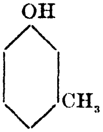
It is estimated that about one-third of all the β-naphthol produced is consumed in the synthesis of β-phenylnaphthyl amine. This compound probably is the most widely used antioxidant for both natural and synthetic rubber.

Alkylated Phenols

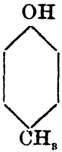
Cresols.—The cresols can be considered as hydroxy derivatives of toluene or as methyl derivatives of phenol. They are obtained from coal tar. As is true for any disubstitution product of benzene, there are three cresol isomers—ortho, para, and meta. A mixture of the three isomers is known as "cresylic acid." One use of this product is in the solvent extraction of lubricating oils.



o-Cresol



m-Cresol

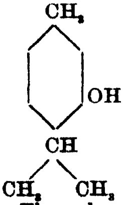


p-Cresol

The crude mixture of cresols separated from coal tar is known as creosote oil, and is employed as a wood preservative for railroad ties, telephone poles, bridge trestles, mine timbers, wharves, and other waterfront structures. It acts as a waterproofing agent, and is toxic to wood-rotting fungi and termites. In moist, warm, tropical climates, termites are a menace to all wooden structures. Treatment with creosote is the means most often used to protect wood from these pests.

The cresols are stronger disinfectants than are the phenols, and they are less toxic to man. They are only slightly soluble in water, but the addition of soap renders them water soluble. "Lysol" and "Cresoline" are disinfectants that contain cresols and soap. The pure isomers usually are not separated from the coal tar distillate, but are prepared from other compounds. m-Cresol is said to be a stronger disinfectant than are the other isomers. Another use of cresols is in the manufacture of synthetic resins. The combined production of o-, p-, and m-cresols amounted to over 60,000,000 pounds in 1940.

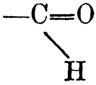
Thymol.—Thymol, or 3-hydroxyl-1-methyl-4-isopropylbenzene, is a pleasant smelling, crystalline compound obtained from the oils of thyme and mint.



Thymol

It is used as an antiseptic in toothpastes and mouthwashes. It is effective in removing hookworms from the intestinal tract.

Aromatic Aldehydes

The aromatic aldehydes contain the same functional group,  $-\mathrm{C}(=\mathrm{O})\mathrm{H}$, as the aliphatic aldehydes, and many of their reactions

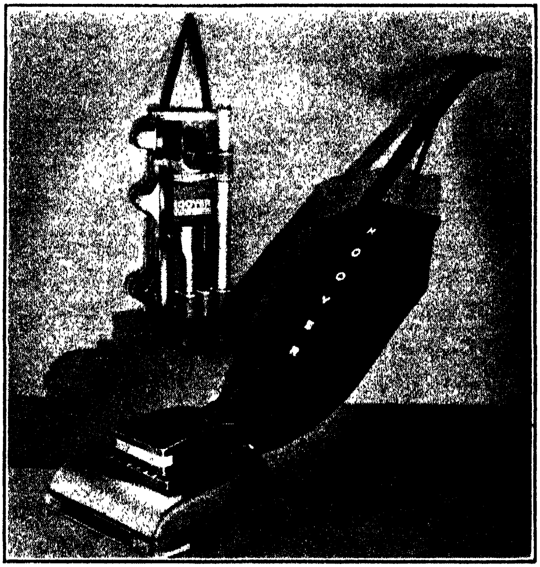


Fig. 62*A*.—*See opposite page for legend.*

are similar to those of the aliphatic aldehydes. The aromatic aldehydes can contain the functional group attached to one of the carbons in the benzene ring, or attached to a carbon in a side chain. The class of aldehydes in which the aldehyde group is separated from the benzene ring by one or more carbon atoms undergoes reactions so similar to the aliphatic aldehydes that further consideration of this group will be omitted.

Benzaldehyde, C_6H_5CHO.—The simplest purely aromatic aldehyde is benzaldehyde. It is a constituent of amygdalin, a naturally occurring glucoside found in bitter almonds and in the kernels of many fruits, such as cherries, peaches, and plums. The characteristic odor of the oil of bitter almonds is due to benzaldehyde. Benzaldehyde can be obtained from a mixture of water and ground peach pits or almonds that have been allowed to stand. An enzyme, emulsin, present in the mixture liberates benzaldehyde. Amygdalin yields glucose, hydrocyanic acid, and benzaldehyde on hydrolysis.

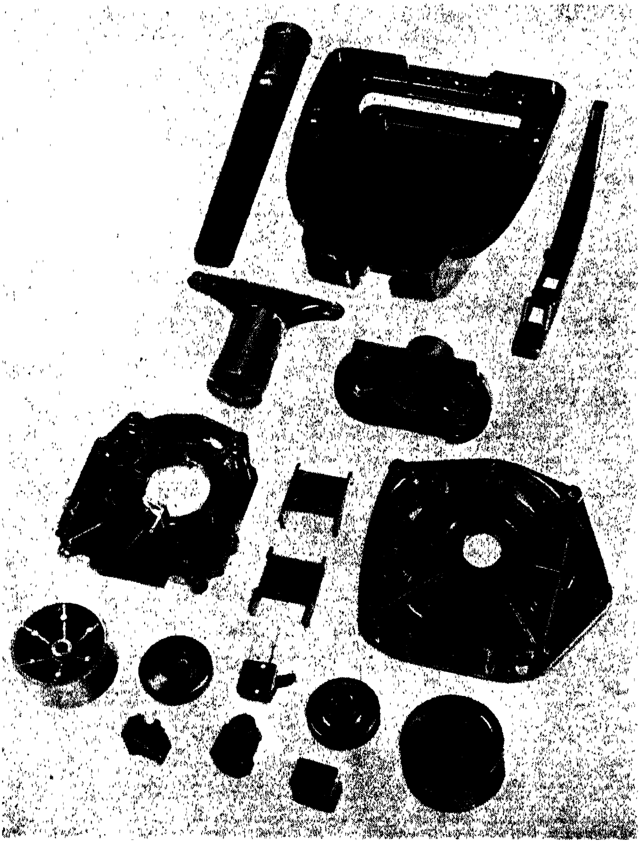


Fig. 62B.—Cresols and phenols are constituents of shock-resistant plastic materials, such as suction sweeper parts. In addition to being shock resistant, these materials produce articles with a high surface luster, and, because of their ease of moldability, are well adapted to the manufacture of pieces of intricate design. (Courtesy of the Bakelite Corporation.)

Preparation.—Benzaldehyde can be prepared from benzyl alcohol, $C_6H_5CH_2OH$, by a method analogous to that used for the preparation of the aliphatic aldehydes from primary alcohols. The aliphatic alcohols are abundant, and accordingly, they are the logical starting point for the preparation of aliphatic aldehydes. However, the aromatic hydrocarbons are more abundant than the aromatic alcohols, and, consequently, are the most frequently used compounds for the preparation of the aromatic aldehydes.

1. Toluene, which is an abundant aromatic hydrocarbon, is a convenient starting point for the synthesis of benzaldehyde. One method for the oxidation of toluene depends on the use of chromyl chloride. Chromyl chloride dissolved in carbon disulfide is added slowly to a flask containing a carbon disulfide-toluene solution. The flask is cooled in ice water to prevent the reaction from becoming too vigorous. An intermediate product is formed; on decomposition with water it yields the aldehyde.

$$\underset{\text{Toluene}}{C_6H_5CH_3} + \underset{\substack{\text{Chromyl}\\ \text{chloride}}}{2\ CrO_2Cl_2} \rightarrow \underset{\text{Intermediate product}}{[C_6H_5CH(OCrCl_2OH)_2]}$$

$$C_6H_5CH(OCrCl_2OH)_2 + 3\ H_2O \rightarrow \underset{\text{Benzaldehyde}}{C_6H_5CHO} + 2\ CrO(OH)_2 + 4\ HCl$$

This method of preparing benzaldehyde is not used widely because of the inflammability of carbon disulfide and the explosive nature of the intermediate compound.

2. Toluene can be oxidized with cerium dioxide in sulfuric acid. Cerium dioxide has the valuable property of oxidizing toluene to the aldehyde stage, but no further.

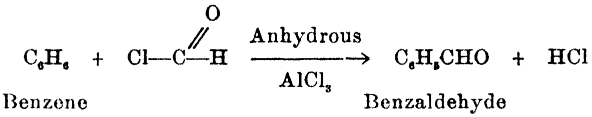
$$\underset{\text{Toluene}}{C_6H_5CH_3} \xrightarrow[H_2SO_4]{CeO_2} \underset{\text{Benzaldehyde}}{C_6H_5CHO}$$

3. Industrially, toluene is oxidized to benzaldehyde with manganese dioxide in 65 per cent sulfuric acid at 40° C. The reaction can easily go too far to produce benzoic acid, whereas the two foregoing reactions do not proceed past the aldehyde stage.

$$C_6H_5CH_3 \xrightarrow[MnO_2,\ 40^\circ\ C.]{65\%\ H_2SO_4} C_6H_5CHO + H_2O$$

4. The hydrolysis of dihalogen derivatives of toluene yields benzaldehyde. Benzyl chloride, formed by the chlorination of toluene in the presence of sunlight, is hydrolyzed with water in the presence of milk of lime. The function of the calcium hydroxide is to neutralize the hydrochloric acid formed.

5. A general method of preparing aldehydes involves the action of anhydrous carbon monoxide and hydrochloric acid on benzene in the presence of anhydrous aluminum chloride, which acts as a catalyst. The hydrochloric acid and carbon monoxide yield formyl chloride, which then combines with a hydrogen of the benzene ring to form benzaldehyde and hydrochloric acid. This is known as *Gattermann's reaction.*

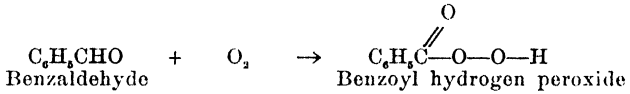


$$\underset{\text{Benzene}}{C_6H_6} + Cl{-}\overset{\overset{O}{/\!\!/}}{C}{-}H \xrightarrow[AlCl_3]{\text{Anhydrous}} \underset{\text{Benzaldehyde}}{C_6H_5CHO} + HCl$$

Benzaldehyde that is to be used for the preparation of flavors and perfumes is prepared by one of the first three methods, because some chlorine derivatives are likely to remain in the benzaldehyde if it is made from one of the chlorinated derivatives. Large quantities of benzaldehyde are consumed in the preparation of dyes, and for this use the benzaldehyde prepared by method 4 is suitable.

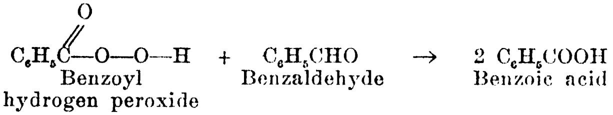
Properties.—Benzaldehyde is a liquid that is soluble in water to the extent of 0.5 per cent; it is soluble in ether in all proportions. The differences between the aliphatic aldehydes and the aromatic aldehydes are not as pronounced as the differences between alcohols and phenols. Benzaldehyde is similar to the aliphatic aldehydes in that it forms a slightly soluble crystalline sodium bisulfite addition product. It reacts with hydroxylamine to form oximes, and with phenylhydrazine to form hydrazones. It reduces combined silver to the metallic form. It does *not* reduce hot Fehling's solution.

One of the most characteristic reactions of benzaldehyde is its susceptibility to oxidation. In the foregoing methods for preparing benzaldehyde, the distillation from the reaction mixture usually is carried out in an atmosphere of carbon dioxide to prevent oxidation to benzoic acid. The oxidation of benzaldehyde proceeds in several steps. Initially, it combines with a molecule of oxygen to form an unstable compound known as benzoyl hydrogen peroxide, or perbenzoic acid.



$$\underset{\text{Benzaldehyde}}{C_6H_5CHO} + O_2 \rightarrow \underset{\text{Benzoyl hydrogen peroxide}}{C_6H_5\overset{O}{\overset{/\!/}{C}}{-}O{-}O{-}H}$$

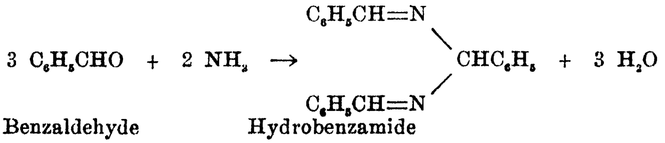
Under ordinary conditions the peroxide breaks up, yielding benzoic acid and an atom of active oxygen. This active oxygen can oxidize another molecule of benzaldehyde; or, if other oxidizable substances are present, they are converted to oxidation products.



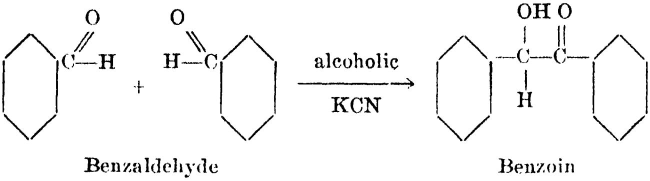
$$\underset{\substack{\text{Benzoyl}\\\text{hydrogen peroxide}}}{C_6H_5\overset{O}{\overset{/\!/}{C}}{-}O{-}O{-}H} + \underset{\text{Benzaldehyde}}{C_6H_5CHO} \rightarrow \underset{\text{Benzoic acid}}{2\ C_6H_5COOH}$$

This self oxidation (auto-oxidation) is not peculiar to benzaldehyde, for a number of substances appear to undergo oxidation by a similar mechanism. The oxidative rancidity of fats may involve a similar type of reaction. The air oxidation of aldehydes, as well as the oxidative rancidity of fats, can be retarded by the addition of a small amount of an easily oxidized material, such as hydroquinol.

Benzaldehyde differs from the aliphatic aldehydes in its reaction with ammonia. Whereas aliphatic aldehydes give aldehyde ammonia, three molecules of benzaldehyde react with two molecules of ammonia to give hydrobenzamide.



Heating with alcoholic potassium cyanide causes two molecules of benzaldehyde to combine to form a hydroxyketone compound. This is known as the *benzoin condensation.*



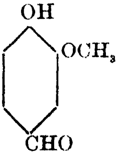
This reaction is similar in some respects to the aldol condensation of aliphatic aldehydes, except that benzoin is a ketonic alcohol instead of an hydroxy aldehyde.

Most aliphatic aldehydes form gummy resins when they are heated with 10 per cent sodium hydroxide, but benzaldehyde gives the Cannizzaro reaction (page 184) under these conditions. Benzaldehyde and formaldehyde behave similarly in this respect, possibly because neither has a hydrogen atom on an alpha carbon atom.

$$\underset{\text{Benzaldehyde}}{2\ C_6H_5CHO} \xrightarrow{\text{NaOH}} \underset{\text{Benzyl alcohol}}{C_6H_5CH_2OH} + \underset{\text{Benzoic acid}}{C_6H_5COOH}$$

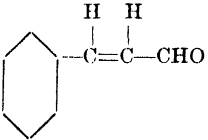
The hydrogen atom para to the hydroxyl group in phenol is more active than the other hydrogen atoms and is more easily substituted. This is true also for aromatic amines. This peculiarity is utilized in the condensation reactions of benzaldehyde to form the triphenyl methane, $(C_6H_5)_3CH$, type of dye (see page 492).

Benzaldehyde is a reactive compound and an important reagent in organic chemistry. Its reactions have been discussed at some length because they are illustrative of the reactions of aromatic aldehydes. Other important natural products also belong to the class of aromatic aldehydes. Vanillin is a methyl ether of pyrocatechuic aldehyde; it is the active component of vanilla extract, and is present in vanilla beans to the extent of about 2 per cent.



Vanillin

Cinnamic Aldehyde.—This unsaturated aldehyde is present in oil of cinnamon. It can be obtained by shaking the oil with a saturated sodium bisulfite solution.

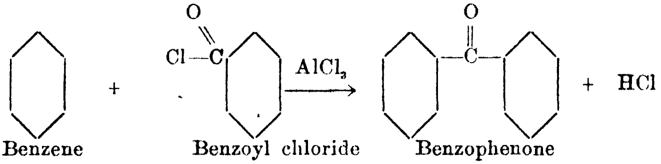


Cinnamic aldehyde

Aromatic Ketones

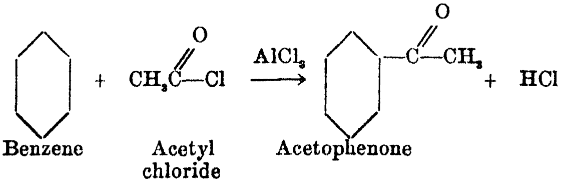
Aromatic ketones can be classified as one of two types: the simple aromatic ketones in which both R groups are aromatic, and the mixed ketones in which one R group is aromatic and the other is aliphatic.

Benzophenone, $C_6H_5COC_6H_5$.—An example of a simple aromatic ketone is benzophenone. It is prepared by the reaction between benzene and benzoyl chloride, the acid chloride of benzoic acid. The reaction is carried out in the presence of anhydrous aluminum chloride as a catalyst (Friedel-Crafts reaction).



Benzophenone is a colorless solid with an agreeable odor. In general, its reactions are similar to those of the aliphatic ketones.

Acetophenone, $C_6H_5COCH_3$.—The simplest aromatic-aliphatic ketone is prepared by the action of acetyl chloride on benzene in the presence of anhydrous aluminum chloride.



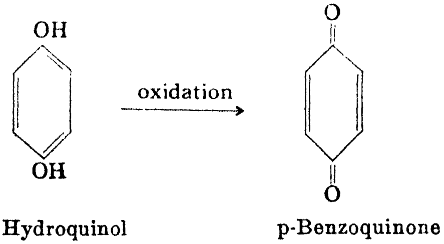
This compound is a colorless oil with a fragrant odor. Because of its use as a soporific and hypnotic, it has been named *hypnone*. Its reactions also are similar to those of the aliphatic ketones. Acetophenone does not, however, give a sodium bisulfite addition product, probably due to the interference of the phenyl group.

Chloroacetophenone, $C_6H_5COCH_2Cl$, is the most commonly used "tear gas."

Quinones

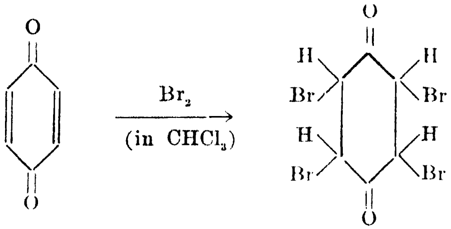
The quinones are discussed with the carbonyl compounds because they react with carbonyl reagents. The ketones contain a carbonyl group attached to one of the carbons in the benzene ring, whereas, in contrast, the quinones contain a carbonyl group as a part of the benzene ring itself.

Benzoquinone, $C_6H_4O_2$.—When hydroquinol is oxidized, benzoquinone, or, more precisely, p-benzoquinone is formed. Benzoquinone is produced also by the oxidation of aniline with sodium dichromate. A series of complex intermediate compounds are formed during the oxidation, but the principal end product is benzoquinone.



Benzoquinone is a yellow crystalline compound that possesses a penetrating, pungent odor. It is only slightly soluble in water, but is soluble in alcohol and ether. It is volatile in steam; that is, when a current of steam is passed through a mixture of water and benzoquinone, the latter is found in the distillate.

Benzoquinone forms both a monoxime and a dioxime, indicating the presence of two carbonyl groups. The compound can react with halogens both by addition and by substitution. In this respect benzoquinone is unique. In fact, this reaction with halogens shows that the typical benzene, or benzenoid, structure no longer is present. The arrangement of the double bonds in parallel fashion is common to all the quinones, and such compounds are said to have a quinoid structure. As we shall see later when we consider dyes, if a compound possesses the quinoid structure, it has color. The quinoid structure is termed a chromophore group. Benzoquinone reacts with bromine in chloroform to form benzoquinone tetrabromide.

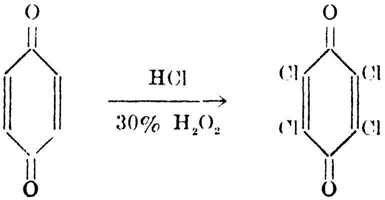


Benzoquinone

Benzoquinone tetrabromide

In this reaction, benzoquinone behaves as though it contained two ethylenic double bonds.

Benzoquinone reacts with hydrochloric acid in the presence of an oxidizing agent to form a tetrahalogen substitution product, chloranil.



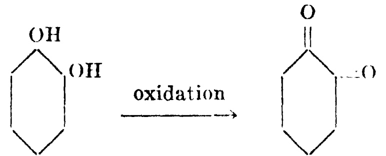
Benzoquinone

Chloranil

Chloranil is an effective oxidizing agent and is used in the dye industry.

If hydroquinol is heated with ferric chloride, quinhydrone, a dark green product, precipitates. This substance contains equal molecular quantities of hydroquinol and benzoquinone in a loose molecular combination. Quinhydrone is used for the determination of hydrogen-ion concentration (quinhydrone electrode).

o-Benzoquinone is prepared from pyrocatechol by oxidation.



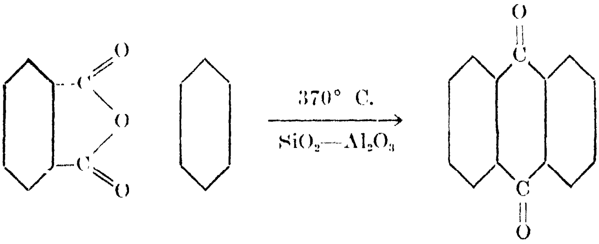
Pyrocatechol o-Benzoquinone

It is a red, crystalline compound without an odor.

m-Quinones are not known.

Anthraquinone.—The carbons in the middle ring of anthracene are oxidized easily to carbonyl groups. Commercially, potassium or sodium dichromate and sulfuric acid are used for this oxidation. Large quantities of anthraquinone are manufactured from phthalic anhydride and benzene. Aluminum chloride is used as a catalyst.

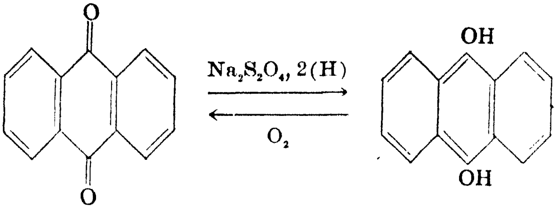
A recent development is the synthesis of anthraquinone by passing benzene and phthalic anhydride at 370° C. over a silica-alumina catalyst.



Phthalic anhydride Benzene Anthraquinone

This method of synthesis can be a one-stage, continuous, or intermittent process, while the one using aluminum chloride is a two-stage batch process.

Anthraquinone is a yellow solid, melting at 285° C. It is a very stable compound and is not attacked easily by nitric acid and oxidizing agents. It is reduced by the action of sodium hydrosulfite ($Na_2S_2O_4$) to the corresponding dihydroxy derivative, anthrahydroquinone.

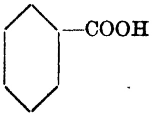


Anthraquinone Anthrahydroquinone

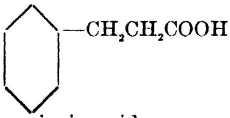
Anthrahydroquinone dissolves in alkali to give a deep red color. This color disappears on shaking with air, since the anthrahydroquinone is oxidized easily back to anthraquinone. An important class of dyestuffs, of which turkey red is an example, is formed by the hydroxy derivatives of anthraquinone.

Aromatic Acids

There are two general types of aromatic acid: in one the carboxyl group is attached directly to the benzene ring, and in the other, the carboxyl group is attached to a side chain.



Benzoic acid
(1)



Phenylpropionic acid
(2)

The monocarboxylic and dicarboxylic acids and their derivatives of type (1) are the most prevalent and important of the aromatic acids.

Benzoic Acid.—The simplest of the aromatic acids has one carboxyl group attached directly to the benzene ring, and is known as benzoic acid, or as benzenecarboxylic acid. It occurs as an ester in gum benzoin (12 to 18 per cent), in various balsams (Tolu and Peru), and in small amounts in cranberries. A pure benzoic acid can be prepared by heating gum benzoin, but a more important commercial method of preparation is by the oxidation of toluene.

$$\underset{\text{Toluene}}{C_6H_5CH_3} \xrightarrow[MnO_2]{H_2SO_4} \underset{\text{Benzoic acid}}{C_6H_5COOH}$$

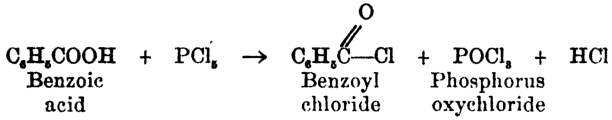
The acid is prepared also by the hydrolysis of benzotrichloride with calcium hydroxide.

$$\underset{\text{Benzotrichloride}}{C_6H_5CCl_3} + 2\ H_2O \xrightarrow{Ca(OH)_2} \underset{\text{Benzoic acid}}{C_6H_5COOH} + 3\ HCl$$

Benzoic acid is a white, crystalline solid that melts at 122° C. It is sparingly soluble in cold water, but is more soluble in hot water. This differential solubility affords a convenient method of purification, since the impure acid can be dissolved in hot water and filtered through a hot funnel. On cooling, the pure acid separates from the filtrate. Benzoic acid is volatile in steam and sublimes at about 100° C. The vapor is irritating to the mucous membranes in the throat and nose, and causes sneezing and coughing. The use of 0.1 per cent benzoic acid as a preservative in foods is allowed by the Food and Drug Administration.

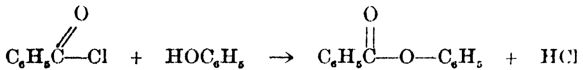
Sodium benzoate, C_6H_5COONa. The sodium salt of benzoic acid is soluble in water and has an antiseptic action. It is used in small quantities as a food preservative in such products as catsup and cider.

Benzoyl chloride, C_6H_5COCl. The acid chloride of benzoic acid is made by the reaction of benzoic acid and phosphorus pentachloride.



$$\underset{\text{Benzoic acid}}{C_6H_5COOH} + PCl_5 \rightarrow \underset{\text{Benzoyl chloride}}{C_6H_5\overset{O}{\overset{\|}{C}}{-}Cl} + \underset{\text{Phosphorus oxychloride}}{POCl_3} + HCl$$

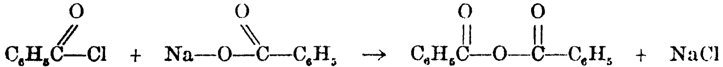
Benzoyl chloride is a liquid, and a lachrymator (causes tear secretion), although it is less irritating than acetyl chloride. It is the reagent commonly used to introduce the benzoyl group into compounds. Such a reaction is termed *benzoylation;* it corresponds to acetylation, or the introduction of the acetyl radical into compounds. The reaction is used to test for the presence of hydroxyl and amino groups in organic compounds. The derivatives that are formed usually are solids; therefore, they can be purified more easily than can a liquid, and, in addition, the melting point of a solid can be determined more easily than can the boiling point of a liquid. Benzoyl chloride reacts in a manner analogous to acetyl chloride, but the benzoyl derivatives are more likely to be solids than are the corresponding acetyl derivatives; thus, the advantage of using benzoyl chloride in certain identification reactions is evident. For example, benzoyl chloride reacts with the hydroxyl group of phenol to form an ester.



$$C_6H_5\overset{O}{\overset{/\!/}{C}}-Cl + HOC_6H_5 \rightarrow C_6H_5\overset{O}{\overset{\|}{C}}-O-C_6H_5 + HCl$$

Benzoyl chloride Phenol Phenylbenzoate

When benzoyl chloride reacts with sodium benzoate, an anhydride is formed.

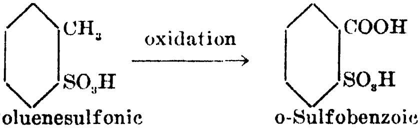


$$C_6H_5\overset{O}{\overset{/\!/}{C}}-Cl + Na-O-\overset{O}{\overset{\backslash\!\backslash}{C}}-C_6H_5 \rightarrow C_6H_5\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-C_6H_5 + NaCl$$

Benzoyl chloride Sodium benzoate Benzoic anhydride

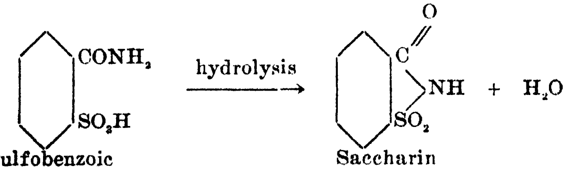
Like benzoyl chloride, the anhydride is used as a benzoylating agent.

Sulfobenzoic acids. The m-sulfobenzoic acids can be obtained by direct sulfonation of benzoic acid. The p- and o- acids, however, must be prepared by the oxidation of p- and o-toluenesulfonic acids.



o-Toluenesulfonic acid o-Sulfobenzoic acid

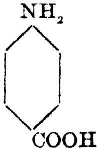
The amide of o-sulfobenzoic acid is of considerable importance, for on loss of water it yields saccharin, an internal amide.



o-Sulfobenzoic acid amide Saccharin

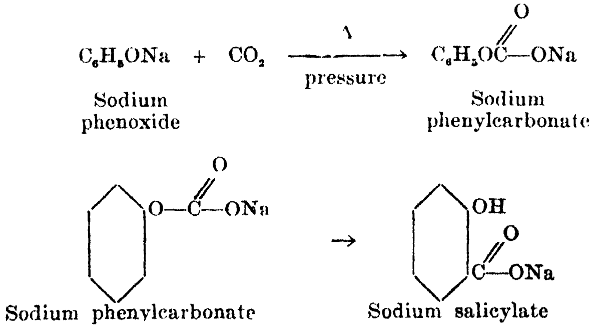
This compound is said to have approximately 500 times the sweetening power of sugar. It has no nutritive value; therefore, it can be used by diabetic patients to increase the palatability of their diets without increasing their supply of dietary sugar. Since the sodium salt is more soluble, it is used sometimes instead of the free saccharin.

p-Aminobenzoic acid. To prepare p-aminobenzoic acid, toluene is nitrated at 50° C., and the p-nitrotoluene is separated *in vacuo.* The p-aminobenzoic acid is obtained by oxidizing the methyl group to the carboxyl group, and by reducing the nitro group to an amino group. p-Aminobenzoic acid recently has been classed as one of the vitamins, since it has been found to be necessary for the normal growths of rats and chicks (see page 721).



p-Aminobenzoic acid

Hydroxy Aromatic Acids.—Of the hydroxy aromatic acids, o-hydroxybenzoic acid, or salicylic acid, is the most noteworthy. Salicylic acid is found as the methyl ester (methyl salicylate) in fairly large amounts in oil of wintergreen. Salicylic acid can be synthesized by heating sodium phenoxide with carbon dioxide under pressure. The sodium phenylcarbonate formed rearranges to form the salt of salicylic acid, which can be acidified to yield the free acid.

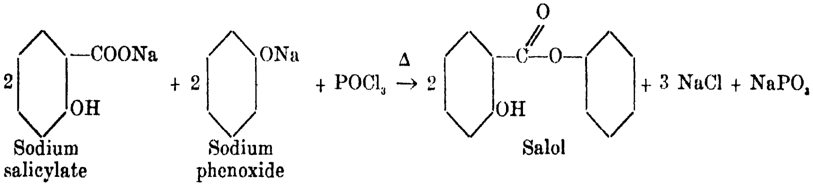


$$C_6H_5ONa + CO_2 \xrightarrow[\text{pressure}]{\Delta} C_6H_5O\overset{\overset{O}{/\!/}}{C}{-}ONa$$

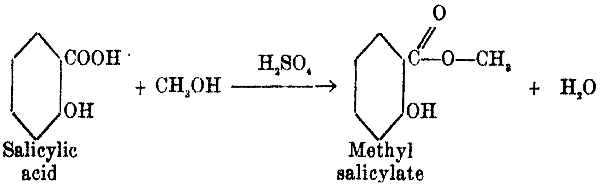
Salicylic acid is a white, crystalline solid, and like benzoic acid, is sparingly soluble in cold water, but more soluble in hot water. When the acid is distilled slowly, it decomposes to yield mainly carbon dioxide and phenol. The acid has powerful antiseptic properties, a fact which leads to its substitution for phenol in certain instances.

Derivatives of Salicylic Acid.—Salicylic acid is a typical acid and forms salts when it reacts with alkalies. The sodium salt possesses antiseptic properties, and, like sodium benzoate, is used as a food preservative. The salt also is effective for the relief of the pain of rheumatic fever.

Salol is a derivative of phenol and salicylic acid. At one time it was thought that this substance would decompose at the pH of the intestine (but not at the acid pH of the stomach) to yield phenol and salicylic acid, which then would act as an intestinal antiseptic. It appears to be true that the compound passes through the stomach unchanged, but it is not effective in producing intestinal antisepsis. Some pills that are meant to pass through the stomach unchanged, and to disintegrate when they reach the intestine, are coated with salol. Stearic acid more often is used for this purpose.

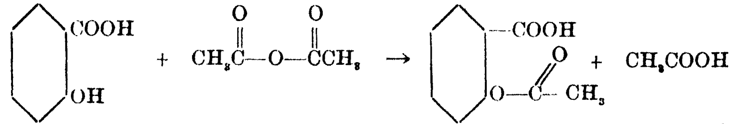


Methyl salicylate is another derivative of salicylic acid that is used in medicine. It is a liquid that has the pleasant odor of wintergreen. It can be prepared by esterifying salicylic acid with methyl alcohol in the presence of sulfuric acid as a catalyst.



This compound is used as a flavoring in toothpastes and candies. It is used as an analgesic in many liniments and salves employed for the treatment of rheumatism, aches, and sprains. It has the rather unusual property of penetrating the unbroken skin.

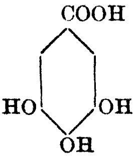
Aspirin is a drug familiar to almost everyone. It is acetylsalicylic acid, and is prepared by heating salicylic acid and acetyl chloride or acetic anhydride.



Salicylic acid Acetic anhydride Aspirin Acetic acid

Enormous quantities of aspirin are produced in the United States. In 1946 the production amounted to 9,926,300 pounds.

Gallic Acid, 3,4,5-Trihydroxybenzoic Acid.—Gallic acid is not a coal tar product. It is produced by the hydrolysis of tannins, which are found in tea, coffee, walnuts, and many other plants. The acid is a trihydroxy derivative of benzoic acid.

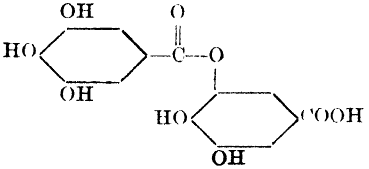


Gallic acid

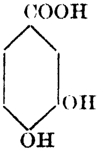
Gallic acid is a solid, soluble in alcohol, ether, and boiling water, but only sparingly soluble in cold water. When it is treated with ferric chloride, it gives a dark blue coloration and a precipitate. If it is heated above 200° C., it decomposes to form carbon dioxide and pyrogallol (see page 442).

Tannin.—Tannin, the glucoside from which gallic acid is obtained, occurs in large amounts (about 50 per cent) in gallnuts. These are pathological growths on the leaves and twigs of oak trees, and are caused by the sting of gall wasps. In addition, tannin is obtained commercially from such substances as hemlock, oak bark, and sumac. Tea, coffee, and cocoa also contain appreciable quantities of tannins, although they do not serve as a commercial source of the compound. In green tea there may be as much as 10 per cent of tannin, while in black tea the amount has been reduced to about 5 per cent.

Tannin contains not only gallic acid, but also other hydroxy aromatic acids, such as digallic acid and protocatechuic acid.



Digallic acid



Protocatechuic acid

Tannins are soluble in water and in ether. The solutions possess an acid, astringent taste. They are responsible for the bitter flavor when tea and coffee are brewed improperly. They react with ferric salts to form a dark bluish-black solution. This property has led to their use in inks. Ordinary writing inks usually consist of (1) an aqueous solution of tannic acid and ferrous sulfate; (2) certain acidic substances (HCl, H_2SO_4); (3) gum; (4) phenol (to prevent moldiness); and (5) an organic dye to give color.

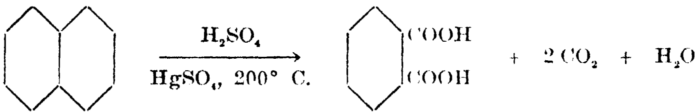
The tannic acid reacts with ferrous sulfate to yield ferrous tannate, a *soluble, colorless* compound. On exposure in thin layers to air, the ferrous tannate is oxidized rapidly to the *black, insoluble* ferric tannate. The organic dye used in the ink gives the original color to the ink, so that the writing is not invisible before the oxidation reaction takes place. This is the transformation that occurs in the familiar blue-black inks. Inks of this type can be decolorized by oxalic acid, which acts to reduce the ferric tannate to the colorless ferrous tannate. This method of ink removal applies only to iron-containing inks. Many inks are now made with organic dyes that are not attacked by oxalic acid. Some of these can be decolorized with hypochlorous acid.

The reaction of tannin with iron salts explains why iron-containing waters make poor tea. The iron in the water combines with the tannins in the water (from the tea extract) to form an insoluble black ferric tannate compound, thus giving an undesirable appearance to the product.

Tannins react with protein. The reaction is used in the tanning of leather. Animal skins under ordinary circumstances rapidly putrefy in the moist state, and on drying become stiff and hard. By tanning, they can be converted into leather that resists decay and is pliable. Formerly, tanning was done by soaking the hides and bark together in vats. The tannin gradually was extracted from the bark and acted on the proteins in the hides. The more modern method is to treat the hides with a solution of tannins prepared from extracts of vegetable materials.

Phthalic Acid and Phthalic Anhydride

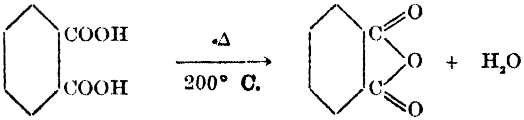
There are three dicarboxylic acid derivatives of benzene, but the o- form, known as o-phthalic acid, or simply as phthalic acid, is of greatest importance. Commercially, it is prepared by the oxidation of naphthalene with sulfuric acid, mercuric sulfate acting as a catalyst.



Naphthalene o-Phthalic acid

The discovery that mercuric sulfate is an effective catalyst for the conversion of naphthalene to phthalic acid was the result of an accident. The action of fuming sulfuric acid on naphthalene was being studied, and in one experiment a thermometer that was being used in stirring the mixture accidentally was broken in the mass. The operators noted that an exceptionally good yield of phthalic acid was obtained, and from this chance happening there developed a practical way of preparing the acid. More recently, molybdenum oxide and vanadium pentoxide have been found also to catalyze the reaction successfully.

o-Phthalic acid forms a stable anhydride when it is heated.



Phthalic acid Phthalic anhydride

Phthalic anhydride is much used in the manufacture of dyes. The peak production of phthalic anhydride during 1945 was 125,033,000 pounds. Phenolphthalein, a familiar indicator used in chemistry, is a product of the reaction between phthalic anhydride and phenol (see page 496 for equation). In alkaline solutions the indicator has a red color; in acid solutions, it is colorless. Phenolphthalein, in addition, is used widely as a laxative.

Phthalic acid, often in the form of its anhydride, is the organic acid most frequently used in the manufacture of alkyd resins. These resins rapidly are increasing in favor as components of high-grade surface coatings, such as enamels and lacquers.

Dibutyl phthalate is one of the most widely used plasticizers for nitrocellulose and other plastics.

Study Questions

1. Write an equation for the preparation of benzyl alcohol by means of the Cannizzaro reaction.
2. Name two aromatic alcohols that are useful in making perfumes.
3. What is the common name for phenol in the liquid form? If it were accidentally spilled on the skin, what would be the most satisfactory way of removing it?
4. What is the chemical composition of "Santophen 20" and for what is it used?
5. What are several aromatic ethers that are used in making perfumes?
6. What is the common name for 2,4,6-trinitrophenol? For what is this compound used?
7. What type of product results when phenol is heated with formaldehyde in the presence of ammonia? Name 5 articles made from this material.
8. Why is phenol not an effective disinfectant for biological material?
9. What are the names and structural formulas of the three dihydroxyphenols? Cite some uses of these compounds.
10. What is Seliwanoff's test?
11. What alkyl derivative of resorcinol has been shown to possess the greatest antiseptic power?
12. What is the common name of 1,2,3-trihydroxybenzene?
13. Write formulas for the two tautomeric forms of phloroglucinol.
14. What are the names of the two isomeric monohydroxy derivatives of naphthalene. For what are these compounds used?
15. What is cresylic acid?
16. What properties of creosote oil make it a valuable wood preservative?

17. The odor of bitter almonds is due to what aromatic compound? How is this product prepared commercially?
18. Write the equation for the benzoin condensation.
19. Name and write formulas for a simple aromatic ketone and a mixed aromatic ketone.
20. In what respect do the quinones differ structurally from the aromatic ketones? Write the formula for benzoquinone.
21. What is quinhydrone and for what is it used?
22. What is the name of the aromatic acid that has one carboxyl group attached directly to the benzene nucleus?
23. What is meant by benzoylation? Write an equation to illustrate your answer.
24. What is the formula for saccharin? To what aromatic acid is it related in structure?
25. What is another name for o-hydroxybenzoic acid?
26. What is the active ingredient in oil of wintergreen that accounts for its flavor and odor? For what is this ingredient used?
27. Write the formula for aspirin.
28. What are some of the aromatic acids in tannins?
29. List four components of an ordinary iron-containing ink? Describe or explain the formation of the final color in blue-black inks.
30. Describe the role played by tannins in the tanning of leather.
31. Why are wet tea leaves effective for the treatment of burns?
32. Write formulas for phthalic acid and phthalic anhydride.

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CHAPTER XVIII

AROMATIC AMINES AND DYES

Introduction.—The aromatic amines are derived principally from the aromatic nitro compounds. As has been mentioned earlier, nitration is one of the characteristic reactions of aromatic compounds. It is by means of this reaction that the nitrogen atom is made to combine directly with the benzene ring. Amines are formed when the nitro compounds are reduced.

There are three classes of aromatic amines—primary, secondary, and tertiary. The basis of the classification is the number of hydrogens in ammonia that are replaced by (R) groups, at least one of which must be an amyl group. This is the same basis as that used for the classification of the aliphatic amines.

Primary Aromatic Amines

Aniline, $C_6H_5NH_2$.—By far the most important primary aromatic amine is aniline. This substance was obtained by Fritzsche in 1841 by heating indigo with potassium hydroxide. He was the first to name the substance aniline (from the French word *anil,* meaning indigo). Industrially, aniline is prepared by the reduction of nitrobenzene with iron and hydrochloric acid.

$$\underset{\text{Nitrobenzene}}{C_6H_5NO_2} + 6HCl + 3\,Fe \rightarrow \underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\substack{\text{Ferrous}\\ \text{chloride}}}{3\,FeCl_2} + 2\,H_2O$$

Only about 2 per cent of the theoretical amount of hydrochloric acid indicated by the foregoing equation is required in the industrial method of preparation. This is explained by the fact that, in the presence of ferrous chloride (formed in the reaction), water acts on the finely ground cast iron to liberate the hydrogen that reduces the nitrobenzene to aniline. Accordingly, the only acid required is for the formation of the ferrous chloride.

$$\underset{\substack{\text{Nitro-}\\\text{benzene}}}{2\,C_6H_5NO_2} + (FeCl_2) + 5\,Fe + 4\,H_2O \longrightarrow \underset{\text{Aniline}}{2\,C_6H_5NH_2} + (FeCl_2) + \underset{\substack{\text{Ferric}\\\text{oxide}}}{Fe_3O_4} + \underset{\substack{\text{Ferrous}\\\text{hydroxide}}}{2\,Fe(OH)_2}$$

As the method is carried out industrially, slightly over two moles of iron and four to five moles of water are employed per mole of the nitro compound to be reduced. The reduction is carried out at the boiling point of the reaction mixture. The aniline formed is distilled from the reduction mixture with steam, separated from the aqueous distillate, and further purified by distillation.

Aniline is readily soluble in benzene, alcohol, and ether, but it is almost insoluble in water. It is a colorless oil when it is pure, but on contact with air it quickly turns brown.

Another industrial method of preparing aniline is by the reaction of ammonia on chlorobenzene. The reaction is carried out in the presence of cuprous oxide at a temperature of 200° to 210° C. and at a pressure of about 900 pounds per square inch.

$$\underset{\text{Chlorobenzene}}{C_6H_5Cl} + \underset{\text{Ammonia}}{2\,NH_3} \xrightarrow[Cu_2O]{200^\circ\text{ C., 900 pounds}} \underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\substack{\text{Ammonium}\\\text{chloride}}}{NH_4Cl}$$

Although only two moles of ammonia are indicated by the equation, in industrial practice six moles of ammonia to one mole of chlorobenzene are employed. The introduction of an amino group by this method often is referred to as *ammonolysis.*

Aniline is toxic to man. Contact with the liquid or inhalation of the vapors should be avoided.

Reactions of Aniline.—1. *Salt formation with acids.* In common with the aliphatic amines aniline possesses basic properties and combines with acids to form salts. These salts are water-soluble, crystalline solids from which the free amine can be regenerated by the action of alkalies. Many compounds used in medicine contain primary aromatic amino groups. As a rule, such compounds are insoluble in water. In order to obtain a water-soluble substance, the primary amino groups are converted to salts.

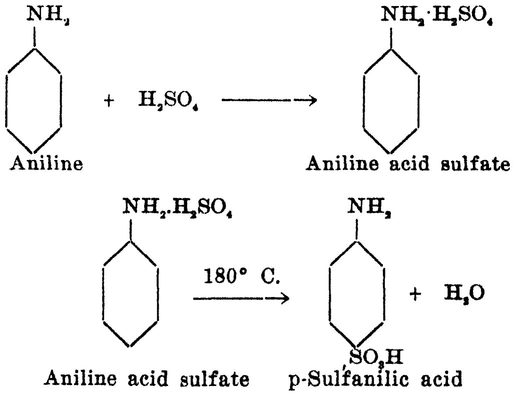
2. *Formation of anilides.* Aniline reacts with organic acids, acid anhydrides, and acid halides to form a class of substituted amides known as *anilides.* Thus, when aniline is heated with glacial acetic acid, acetanilide is formed.

$$\underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Acetic acid}}{CH_3COOH} \xrightarrow{100^\circ\text{ C.}} \underset{\text{Acetanilide}}{C_6H_5NHCOCH_3} + H_2O$$

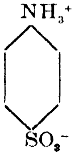
Acetanilide, also known as antifebrin, is used to reduce fever. It is the active agent in many remedies for headache and neuralgia. In hydrogen peroxide solutions acetanilide acts to inhibit the reaction that causes the peroxide to decompose, with the formation of oxygen and water. If it were not for the addition of acetanilide, many dilute solutions of hydrogen peroxide sold for antiseptic purposes would be worthless.

Acetanilide is a typical example of an acyl derivative of a primary aromatic amine. It is a solid, as are most such acyl derivatives. Due to this fact, the acyl derivatives often are used for identification purposes.

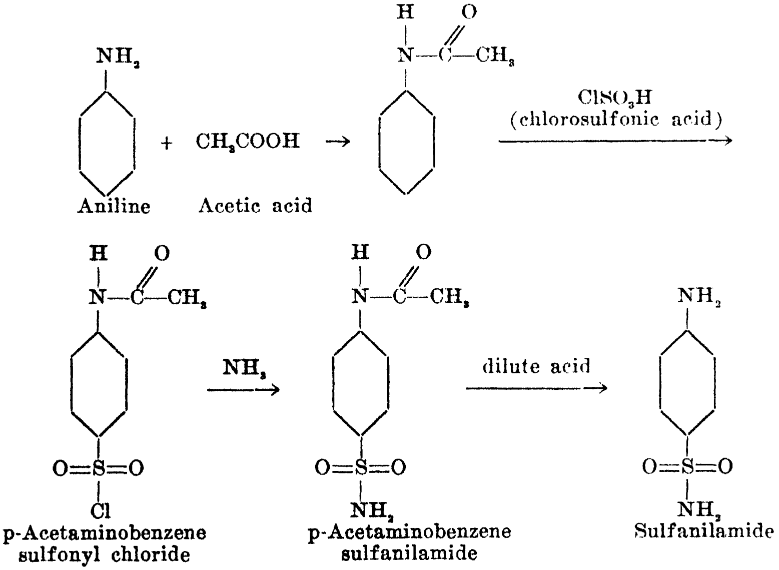
3. *Reaction with sulfuric acid.* When aniline is heated with concentrated sulfuric acid, the salt of the acid is formed first, but on heating this to 180° C., the sulfonic acid enters the ring para to the amino group, forming p-aminobenzenesulfonic acid. The name of this compound has been condensed to p-sulfanilic acid.



p-Sulfanilic acid is a solid that is insoluble in water and in most organic solvents. Its basic properties are so weak that it does not dissolve even in concentrated hydrochloric acid. It is nonvolatile and has no definite melting point; thus, it resembles an inorganic salt more than it does an organic compound. These anomalies are explained best by assuming an inner salt combination between the sulfonic group and the amino group. Such a combination can be represented as follows:



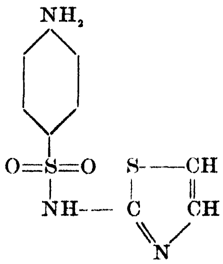
Sulfanilamide (aminobenzenesulfonamide) is a derivative of sulfanilic acid. It can be prepared by the following series of reactions:



Credit for the discovery of the effectiveness of sulfanilamide in the treatment of human disease must go to a number of workers. The observation was made in 1932 by G. Domagk that a dye, Prontosil, given by mouth protected mice against otherwise fatal doses of hemolytic streptococci. This was, perhaps, the first significant observation of a series that led to the discovery of the remarkable curative powers of sulfanilamide. Late in 1935 the French workers Trefouel, Nitti, and Bovet announced that the action of prontosil on microorganisms was due to the fact that the dye was broken down in the body to yield sulfanilamide, which was the therapeutic agent. In 1936 Long, Bliss, and Marshall and their co-workers at Johns Hopkins University confirmed the experimental findings of the European investigations on the therapeutic action of sulfanilamide. The adoption of sulfanilamide as a curative agent for a large number of diseases followed in rapid order. It was found effective in the treatment of puerperal fever, erysipelas, septicemia, scarlet fever, mastoiditis, pneumonia, septic sore throat, streptococcal meningitis, gonorrhea, and gas gangrene. In some cases the administration of the drug was followed by almost unbelievably rapid recoveries.

It soon became apparent, however, that sulfanilamide was not a panacea. Its use frequently was attended by toxic symptoms such as nausea, dizziness, cyanosis, psychoses, and anemia, so that the search for derivatives that would not have these undesirable characteristics and that could be used to combat diseases that did not yield to treatment with sulfanilamide was begun. These researches have shown that the amino group in the derivatives must be para to the sulfonamide group. Meta and ortho amino compounds have no observable therapeutic action.

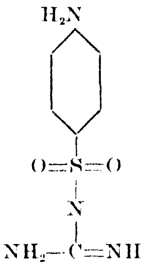
Sulfathiazole is a derivative of sulfanilamide that is particularly valuable in the treatment of staphylococcus in-



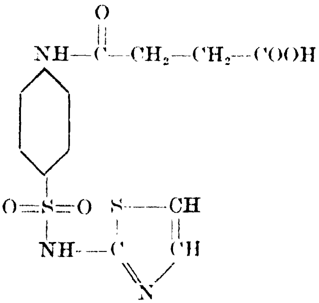
Sulfathiazole

fections. It shows less toxic reaction than sulfanilamide but is more toxic than some of the newer drugs.

Sulfaguanidine and Sulfasuxidine (succinylsulfathiazole) are two derivatives that are poorly absorbed from the intestinal tract. This property makes them useful in the treatment of bacillary dysentery; the high concentration of the drug in the intestinal tract drastically reduces the bacterial count. This same property makes the drugs useful in pre- and postoperative intestinal surgery patients to help diminish gas pains and the possibility of peritonitis and abscess formation. Of the two drugs, Sulfasuxidine is the less toxic.

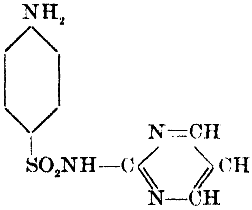


Sulfaguanidine



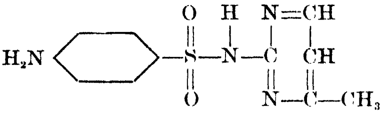
Sulfasuxidine

Sulfadiazine is less toxic than many of the sulfa drugs. It is useful in the treatment of pneumonia and staphylococcic infections.



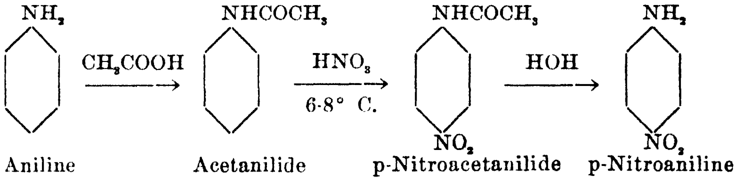
Sulfadiazine

Sulfamerazine is one of the newer sulfa derivatives. It is said to be more quickly absorbed and less rapidly excreted than the other sulfonamides; therefore, the drug can be given successfully in two or three doses daily instead of the customary four to six used for the other sulfa drugs. Studies indicate that the toxicity of sulfamerazine is about the same as for sulfadiazine.

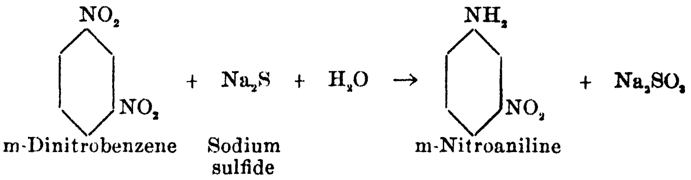


Sulfamerazine

4. *Reaction with nitric acid.* When aniline is treated with concentrated nitric acid, the reaction is mainly that of oxidation, although some nitration does take place. The amino group can be protected from the oxidizing action of nitric acid by acetylation, with the formation of acetanilide. In the nitration of acetanilide, substitution takes place almost entirely in the para position. The amino group is set free by hydrolyzing off the acetyl group.



m-Nitroaniline can be prepared by the reduction of m-dinitrobenzene. If this reduction is carried out with sodium sulfide, only one of the nitro groups is reduced.



The sodium sulfide (dissolved in alcohol) is mixed with an alcoholic solution of m-dinitrobenzene in a steam-jacketed reducer. The reaction mixture is maintained at the boiling temperature for two hours, after which the alcohol is distilled off. The inorganic salt in the solid reaction mixture is dissolved out with water. The suspension from this process is pumped into large filter presses, from which m-nitroaniline is obtained as a moist cake. Drying of this cake is carried out on trays in a vacuum drier.

5. *Halogenation.* The ease of substitution of the nuclear hydrogens* of aniline is analogous to the ease of substitution of nuclear hydrogens in phenol. When aniline is mixed with bromine water, a white solid, 2,4,6-tribromoaniline, separates. The formation of the white precipitate, which is sparingly soluble in water and has a definite melting point, can be used for the identification of aniline.

Aniline resembles the primary aliphatic amines in that it gives the carbylamine reaction (page 297) with chloroform and caustic alkali. The disagreeable odor of the phenylisocyanate is unmistakable.

6. *Oxidation.* Aniline is oxidized easily. The course of the oxidation depends to a large extent on the conditions under which the reaction takes place. If sodium dichromate is added to a solution of aniline and sulfuric acid, a series of colored oxidation products are formed. The reaction culminates in the formation of a complicated mixture of substances known as aniline black. Aniline black is used for staining and protecting the tops of wooden laboratory desks.

Secondary Aromatic Amines

The secondary amines may be of two types: (a) those in which there are alkyl and aryl groups, and (b) those in which there are only aryl groups. Monomethylaniline (N-methylaniline†) is a representative of the first class. It is prepared by heating aniline sulfate with methyl alcohol under pressure in an autoclave. Monomethylaniline, treated with the usual nitrating mixture of nitric and sulfuric acids, yields a nitrated nitramine.

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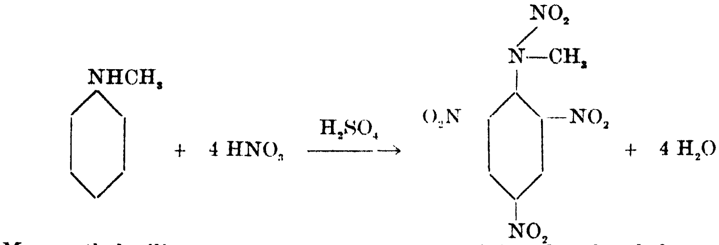
*The carbon atoms in the benzene ring, when considered as a group, often are termed the nucleus. The hydrogens attached to this nucleus are then the nuclear hydrogens.

†This designation is used to indicate that the methyl group is combined with the nitrogen.



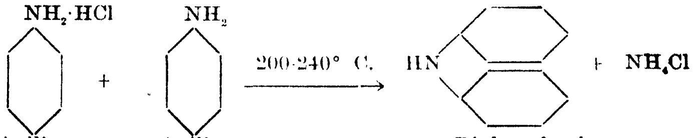
Monomethylaniline

Trinitrophenylmethylnitramine

Trinitrophenylmethylnitramine, also known as tetryl, is used as a "booster" in military explosives. The function of substances used as boosters is to explode between the explosion of the detonator and the main bursting charge, thus increasing the destructive action of the main charge.

A mixture of tetryl and T.N.T. is used as an explosive in torpedoes.

Diphenylamine, $(C_6H_5)_2NH$.—Diphenylamine is an example of a purely aromatic secondary amine. It is prepared by heating aniline hydrochloride with aniline at a high temperature in an autoclave.



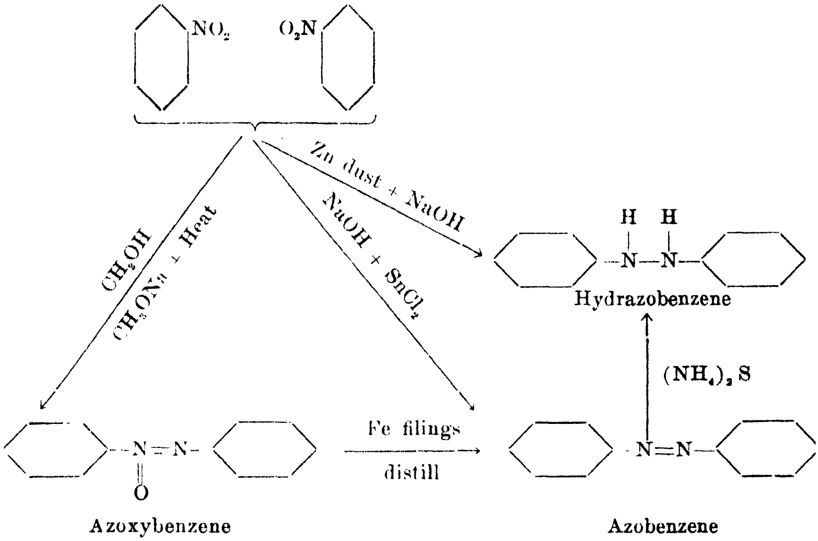
Aniline hydrochloride

Aniline

Diphenylamine

This compound crystallizes in the form of small plates, and has a melting point of 54° C. Diphenylamine is used in smokeless powder as a stabilizer to prevent spontaneous decomposition. A solution of diphenylamine in concentrated sulfuric acid gives a blue color in the presence of nitrates. This is an easy test to perform and a very sensitive one.

Products Resulting From the Reduction of Nitrobenzene in Alkaline Solution.—When the reduction of nitrobenzene is carried out in alkaline solution in the presence of zinc dust and sodium hydroxide, a number of reduction products containing two benzene rings can be obtained by controlling the reducing activity of the system. These compounds, and the reducing agents used to obtain them, are shown in the following diagram:



Hydrazobenzene is the starting material for the preparation of the benzidine dyes, the most widely used dyestuffs for cotton.

Tertiary Amines

Dimethylaniline, $C_6H_5N(CH_3)_2$.—Dimethylaniline is produced by the same type of reaction as that used for the preparation of monomethylamine. The conditions of the reaction, such as the amount of methyl alcohol used and the temperature of the reaction, determine whether monomethylamine or dimethylamine is produced in excess.

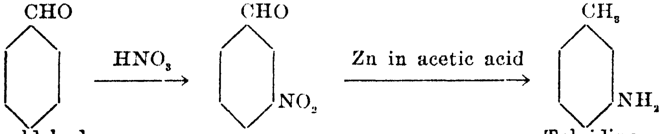
$$\underset{\text{Aniline}}{C_6H_5NH_2} + 2\,CH_3OH \xrightarrow[H_2SO_4]{200^\circ\text{ C., 30 atmospheres}} \underset{\text{Dimethylaniline}}{C_6H_5N(CH_3)_2} + 2\,H_2O$$

Dimethylaniline is a pale yellow, oily liquid that boils at 193° C. The hydrogen para to the dimethylamino group is especially active, and takes part in many reactions used in the preparation of dyes (page 492). In 1940 over seven million pounds of dimethylaniline were manufactured in the United States.

Triphenylaniline, $(C_6H_5)_3N$.—The presence of three negative phenyl groups around the nitrogen atom in diphenylaniline reduces the basicity of the compound to the extent that it no longer forms salts with either hydrochloric acid or sulfuric acid.

Homologues of Aniline

Toluidines, $CH_3C_6H_4NH_2$, o, p, m.—The toluidines are related to toluene in the same way that aniline is related to benzene. As is always the case for disubstituted derivatives of benzene, there are three isomeric toluidines. The o- and p- isomers are made by the reduction of the corresponding nitrotoluenes. m-Toluidine can be prepared from benzaldehyde.



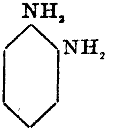
Benzaldehyde m-Toluidine

Only the important end products are given in the foregoing reaction. The student should write out the completed and balanced equation for each step of the synthesis.

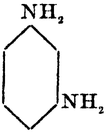
Xylidines, $C_6H_3(CH_3)_2NH_2$.—The xylidines are the corresponding amino derivatives of xylene. They are used in the preparation of dyes.

Diamines

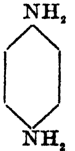
An important class of aromatic compounds that contains two primary amino groups is the phenylene* diamines. There are three isomers.



1, 2-Diaminobenzene



1, 3-Diaminobenzene



1, 4-Diaminobenzene

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*The phenylene radical is derived from benzene by the loss of two hydrogens. It corresponds to the methylene radical, $—CH_2—$, in the aliphatic series.

These diamino derivatives of benzene are all solids that dissolve easily in water. o-Phenylenediamine is prepared by the reduction of o-nitroaniline with zinc dust and alkali. m-Phenylenediamine is made by the reduction of m-dinitrobenzene. This reduction is carried out in industry with iron and hydrochloric acid. m-Phenylenediamine finds limited application as a hair and fur dye.

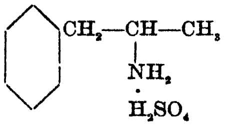
Other Amines

Benzylamine, $C_6H_5CH_2NH_2$.—The amino compounds in which the amino group is attached to a side chain are isomeric with the toluidines, but the properties of the two classes of compounds differ markedly. Benzylamine is prepared by the action of ammonia on benzyl chloride.

$$\underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} + NH_3 \rightarrow \underset{\text{Benzylamine}}{C_6H_5CH_2NH_2} + HCl$$

Benzylamine is a liquid with an ammoniacal odor. It dissolves in water to give a strongly alkaline solution. In this and in other properties it resembles the aliphatic amines. The influence of the negative phenyl group in reducing the basicity of the nitrogen atom, as for example in aniline, almost disappears when the phenyl group is separated from the nitrogen atom by a carbon atom. The properties of benzylamine are more in keeping with the properties of a compound resulting from the replacement of one of the hydrogen atoms in methylamine by a phenyl group.

Benzedrine, β-Phenylisopropylamine.—Benzedrine in the form of its sulfate is a stimulant for the central nervous system, and, as the free base, is used to constrict the mucous membrane of the nasal passages.



Benzedrine sulfate

It has given encouraging effects in the symptomatic management of manic-depressive psychoses. The so-called "pep pills'' taken by some students in order to stay awake while studying for examinations are benzedrine sulfate. The use of this substance does allow some students to work for long periods of time without sleep, but the consumption of the drug may be dangerous, since it causes a marked increase in the blood pressure and in the pulse rate of many persons. Collapse and hysteria have resulted from its use. *If a person knows that in his case no ill effects result from the ingestion of the compound,* a useful application of the drug is to take it if he must drive at night when he is very tired. The drug helps to keep him awake, and thus aids in preventing dangerous accidents.

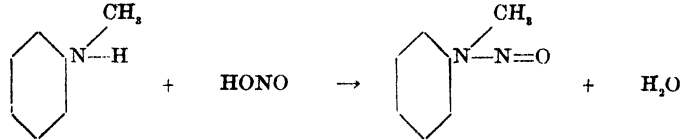
Reaction of Nitrous Acid With Aromatic Amines

Primary aromatic amines react with nitrous acid to form a class of derivatives known as *diazonium compounds.* These compounds are very different from the products obtained by the reaction of nitrous acid with primary aliphatic amines, which are alcohols and gaseous nitrogen (see page 297).

$$\underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Nitrous acid}}{HNO_2} \xrightarrow{0^\circ\text{-}5^\circ\text{ C.}} \underset{\text{Benzene diazonium chloride}}{C_6H_5N_2Cl} + 2\,H_2O$$

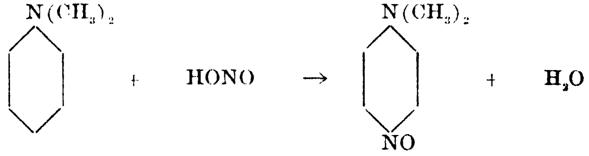
This reaction with nitrous acid is known as diazotization. It must be carried out at a low temperature to prevent decomposition of the diazonium compound. A separate section (page 480) will be devoted to the numerous reactions of benzene diazonium chloride. One of these reactions is especially important in the preparation of a number of dyes.

Secondary aromatic amines, as well as secondary aliphatic amines, react with nitrous acid to form nitroso derivatives. The formation of the nitroso derivative of monomethylaniline is represented by the following equation:



Monomethylaniline Nitrosomethylaniline

Tertiary aliphatic amines do not react with nitrous acid except to form salts. Aromatic tertiary amines, however, form nitroso derivatives. The absence of hydrogen on the nitrogen atom precludes the possibility of forming nitrogen derivatives, but as we have seen in other cases, the para hydrogen atom is especially active, and substitution takes place at this point.



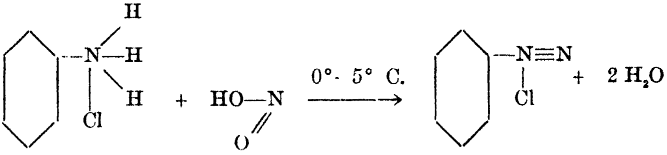
Dimethylaniline Nitrous acid p-Nitrosodimethylaniline

p-Nitrosodimethylaniline is a green solid that is only slightly less basic than the original amine. This nitroso derivative of dimethylaniline is useful in the synthesis of dyes.

Diazo Compounds

The term *diazo* is a general one used to indicate the presence of two nitrogen atoms in the molecule. The term *azo* comes from the French word *azote,* meaning nitrogen. The diazo compounds rank in importance with the Grignard reagent and acetoacetic ester as reagents in organic syntheses. The preparation of a large and important class of dyes, the azo dyes, would not be possible without the diazo compounds.

The diazonium compounds, one of the classes of diazo compounds, are prepared, as we have seen, by the reaction of nitrous acid on primary aromatic amines. In practice, the amine is dissolved in concentrated mineral acid in the proportion of about two and a half moles of the acid to one mole of the amine. This is necessary since there must be sufficient acid to form the salt of the amine, to generate nitrous acid, and still leave an acid solution. The nitrous acid is generated in the reaction mixture by adding slowly a 10 to 20 per cent solution of sodium nitrite. It is necessary to keep the reaction mixture at a low temperature, 0° to 5° C., because diazonium compounds decompose above 8° to 10° C.

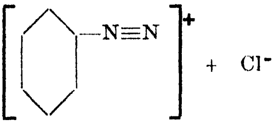


Aniline hydrochloride

Benzenediazonium chloride

The diazonium salts seldom are isolated, since the dry salts are dangerously explosive when they are heated or struck a slight blow. In solution, the diazonium salts are quite safe to handle; therefore, their reactions are carried out in the solutions in which they are prepared.

The diazonium salts resemble the ammonium or quaternary ammonium salts in that (1) they are soluble in water, and (2) they ionize in aqueous solution. This saltlike character is indicated by the *onium* ending. The diazonium compounds, like the ammonium salts, contain pentavalent nitrogen. The resemblance of benzenediazonium chloride to ammonium compounds is emphasized further by the following formula for benzenediazonium chloride in aqueous solution:



Reactions of the Diazonium Compounds.—The reactions of the diazonium compounds can be divided into two large classes: (a) the replacement reactions, and (b) the "coupling reactions."

Replacement reactions. The ease with which the diazonium group can be replaced by other groups or elements renders them very useful in synthetic organic chemistry. It is important to note that in this type of reaction the nitrogen is evolved as elementary nitrogen. Some of the replacement reactions of benzenediazonium chloride are:

Replacement by chlorine. The diazonium group is replaced by chlorine when cuprous chloride is added to a solution of benzenediazonium chloride.

$$\underset{\substack{\text{Benzenediazonium}\\\text{chloride}}}{C_6H_5N_2Cl} \xrightarrow{Cu_2Cl_2} \underset{\text{Chlorobenzene}}{C_6H_5Cl} + N_2$$

This is known as the Sandmeyer reaction. If the replacement is brought about in the presence of finely divided powdered copper, it is known as the Gattermann reaction.

Replacement by bromine. In a similar fashion the diazonium group can be replaced by bromine.

$$C_6H_5N_2Cl \xrightarrow{Cu_2Br_2} C_6H_5Br + N_2$$

Replacement by iodine. Cuprous salts are not necessary for the replacement of the diazonium group by iodine. If potassium iodide is allowed to react with benzenediazonium chloride, iodobenzene separates. This is one of the most convenient methods of introducing iodine into the aromatic nucleus.

$$C_6H_5N_2Cl \xrightarrow{KI} C_6H_5I + N_2$$

Replacement by cyanogen. The cyanogen or cyanide group ($C\equiv N$) can be substituted for the diazonium group by the addition of cuprous cyanide.

$$\underset{\substack{\text{Benzenediazonium}\\\text{chloride}}}{2\,C_6H_5N_2Cl} + \underset{\substack{\text{Cuprous}\\\text{cyanide}}}{Cu_2(CN)_2} \xrightarrow{KCN} \underset{\substack{\text{Phenyl}\\\text{cyanide}}}{2\,C_6H_5CN} + \underset{\substack{\text{Cuprous}\\\text{chloride}}}{Cu_2Cl_2} + 2\,N_2$$

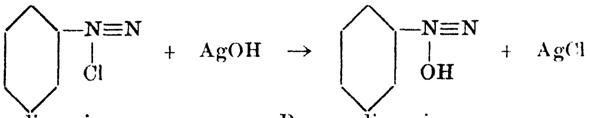
It will be remembered that the cyanide group can be hydrolyzed to the carboxyl group; thus the preceding reaction affords a convenient method for adding the carboxyl group to the benzene ring.

Replacement by hydroxyl group. If an aqueous solution of a benzenediazonium salt is warmed, nitrogen is evolved and a phenol is formed. This is the reaction that takes place if the temperature during diazotization is not kept below 5° C.

$$C_6H_5N_2Cl + H_2O \rightarrow C_6H_5OH + N_2 + HCl$$

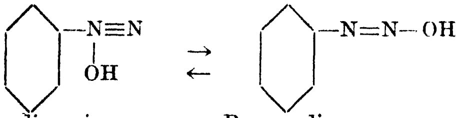
Benzenediazonium chloride   Phenol

Tautomerism of diazonium compounds. Before considering the coupling reactions, we must digress to consider the form of the diazonium salts that takes part in these reactions. If a solution of benzenediazonium chloride is treated with silver hydroxide, silver chloride precipitates, and a strongly alkaline solution results. The properties of this strong base resemble those of quaternary ammonium hydroxides.



Benzenediazonium chloride   Benzenediazonium hydroxide

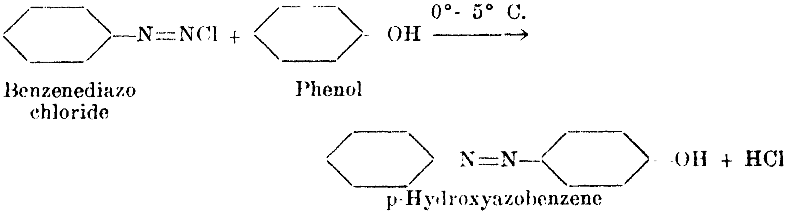
By the action of hydrochloric acid, benzenediazonium chloride again is formed. The hydroxide itself has not been isolated. If the solution of benzenediazonium hydroxide is treated with sodium hydroxide, the organic base becomes weaker, until finally it behaves like a weak acid; that is, it forms a sodium salt. This change in properties is believed to be due to a rearrangement within the molecule. The structure of the compounds formed can be represented as:



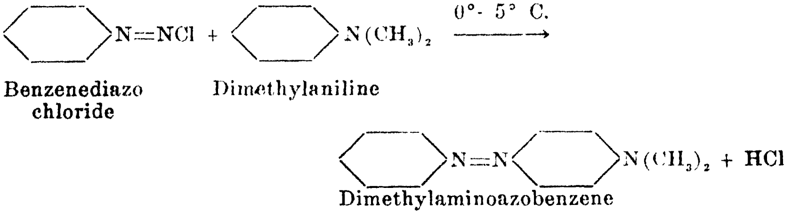
Benzenediazonium hydroxide   Benzenediazo hydroxide

It will be noted that both the nitrogen atoms are trivalent in the benzenediazo hydroxide. This tautomerism explains the reaction of benzenediazonium salts in alkaline solution, and also the mechanism for the coupling reaction used for the formation of dyes.

Coupling reaction. During the coupling reactions, the nitrogen atoms are retained and the azo linkage, —N=N—, is formed. From this fact it seems that the diazo form of benzenediazonium chloride, $C_6H_5N{=}NCl$, rather than the diazonium form, $C_6H_5\underset{\underset{Cl}{|}}{N}{\equiv}N$, takes part in these reactions. In neutral or alkaline solution, aromatic amines and phenols undergo the coupling reaction with diazo salts. This reaction involves a para position unless this position already is occupied, in which case the coupling can take place at the ortho position. Meta coupling does not occur. The coupling reaction with phenol can be represented as follows:



Tertiary amines also couple in the para position.

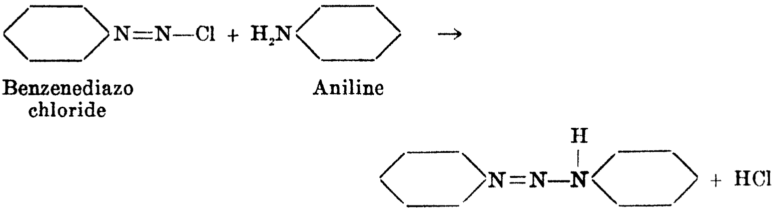


The term *azo,* instead of diazo, is used in the naming of the compounds formed in order to indicate that there is one nitrogen atom for each ring, and not two nitrogen atoms associated with one ring as in the diazo salts. The correctness of the formula given by the coupling reaction is demonstrated by the products formed on reduction.

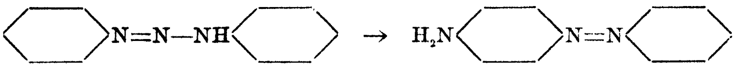
$$\underset{\text{Dimethylaminoazobenzene}}{C_6H_5N{=}NC_6H_5N(CH_3)_2} \xrightarrow{\text{reduction}} \underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\substack{\text{p-Aminodimethyl}\\ \text{aniline}}}{NH_2C_6H_5N(CH_3)_2}$$

Primary amine groups are formed at the point where the two nitrogens were joined.

The diazo salts also couple with primary and secondary amines to form diazoamino compounds. A typical reaction of this class is the reaction of benzenediazo chloride with aniline.

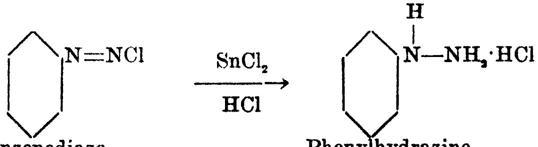

Benzenediazo chloride
Aniline
Diazoaminobenzene

The most important reaction of diazoaminobenzene is its transformation to p-aminoazobenzene when it is heated with aniline hydrochloride, or with an excess of hydrochloric acid.


Diazoaminobenzene
p-Aminoazobenzene

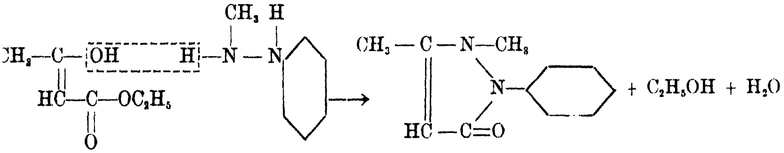
This compound is a yellow azo dye, although it is not used for dyeing purposes because the color is not permanent.

The mild reduction of benzenediazo salts in acid solution with stannous chloride yields phenylhydrazine hydrochloride.


Benzenediazo chloride
Phenylhydrazine hydrochloride

The free base that can be obtained by the treatment of phenylhydrazine hydrochloride with sodium hydroxide is a liquid with an unpleasant odor. Exposure to air causes it to darken. The vapors of phenylhydrazine are toxic, and undue exposure to the fumes should be avoided. The importance of phenylhydrazine in the characterization of aldehydes, ketones, and the sugars already has been emphasized.

Antipyrine is obtained by condensing methyl phenylhydrazine with the enol form of acetoacetic ester.



Acetoacetic ester

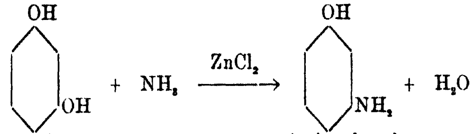
Methyl phenylhydrazine

Antipyrine

Antipyrine originally was introduced as an antipyretic (to reduce fever). Now it is a component of many of the mixtures sold to the public for the relief of pain.

Aminophenols

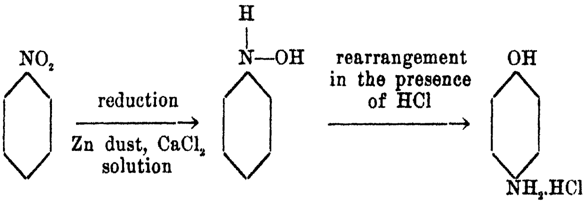
The aminophenols are prepared by the reduction of the corresponding nitrophenols or by the action of ammonia on the dihydroxyphenols, using zinc chloride as a catalyst. m-Aminophenol can be prepared in this way from resorcinol.



Resorcinol

m-Aminophenol

p-Aminophenol can be synthesized from nitrobenzene by the following method:


reduction
Zn dust, $CaCl_2$ solution
rearrangement in the presence of HCl

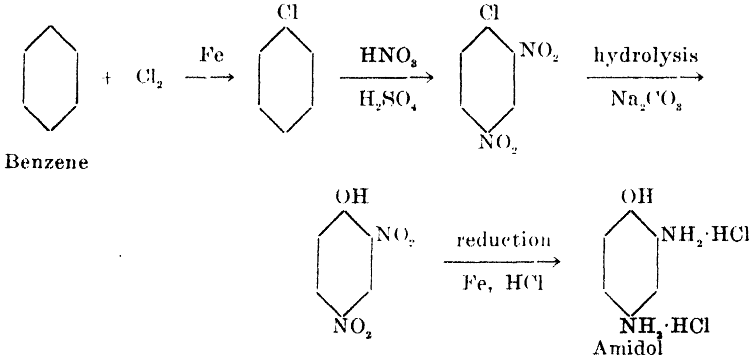
Nitrobenzene

Phenylhydroxylamine

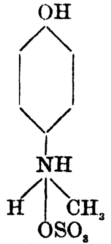
p-Aminophenol hydrochloride (Rodinal)

p-Aminophenol hydrochloride is employed in photography as a developer under the name of Rodinal. The 1,4- derivatives of the p-aminophenol type of compound are oxidized very readily, especially in alkaline solution. Due to this property, they are valuable as photographic developers.

Amidol also is used as a photographic developer. It can be prepared from benzene in the following manner:



Another one of the amino phenolic type of photographic developers is metol, whose sulfate has the formula illustrated below.



Metol sulfate

These compounds, which are used as photographic developers, illustrate a property that has been pointed out several times before: namely, that amino, hydroxyl, and methyl groups in the para and ortho positions markedly increase the reactivity of an aromatic compound.

Photographic film consists of an intimate mixture of silver bromide and gelatin on a transparent cellophane sheet. On exposure to light the silver bromide is reduced partially to metallic silver, the extent of the reduction being dependent on the intensity of the light. The function of a photographic developer is to continue the reduction, which already has been started by the action of light. The reduction proceeds most rapidly and deposits the most silver where the illumination was the brightest. Thus a plate is formed that is darkest where the light was most intense. On account of this reversal the plate is called a negative. The silver bromide that has not been exposed to light is not affected by the developer. To prevent the gradual reduction of the remaining unchanged silver bromide to silver by the action of light, the silver bromide is dissolved out by soaking the film in "hypo," $Na_2S_2O_3$.

Dyes

Although the definition is not entirely satisfactory, we can define a dye as a compound that is capable of imparting permanent color to a textile or other solid material.

Ordinary white light passed through a glass prism breaks up into its component colors, which are known as a spectrum. Substances are capable of absorbing or reflecting light. The color of a substance is dependent on the kind of light that it reflects; that is, on the kind of light that reaches our eyes. The absorption of light is dependent on the chemical structure of the substance absorbing the light. From a more fundamental standpoint, this absorption of radiant energy is dependent on an unstable arrangement of electrons in the molecule.

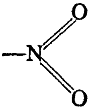
Up to the middle of the last century all dyes were obtained from naturally occurring substances. The first dye to be synthesized, *mauve,* was prepared in 1856 in a private laboratory by William Henry Perkin, then a lad only 18 years of age. The preparation, however, was quite unintentional. Perkin, working during his Easter vacation, was trying to prepare quinine by the oxidation of aniline. As sometimes happens to organic chemists, he obtained a black, tarry mass instead of the beautifully crystalline product he anticipated. He was washing out the tar with alcohol when he noted a violet color in the alcoholic solution. It was an indication of his future greatness that the curiosity of this 18-year-old investigator led him to isolate the colored substance and to try it as a dye. He realized the commercial importance of his discovery, and later he founded a very profitable dye industry in England.

The discovery by Perkin that a dye could be made in the laboratory from substances that possess no color was the impetus for feverish attempts by organic chemists to synthesize other dyes. An important event in these attempts was Kekulé's announcement of a structural formula of benzene. Now there was some theoretical basis for aromatic chemistry. When Perkin discovered his dye, the structural formula of aniline was not even known. An indication of the influence of the development of the theoretical side of organic chemistry was the synthesis for the first time of a naturally occurring dye by Graebe and Liebermann in 1868. This dye, alizarin, had been obtained formerly only from the madder root. Other chemists were working on a similar process. In fact, Graebe and Liebermann filed their patent for a commercial method of manufacturing alizarin on June 25, 1869, one day before Perkin filed a patent for the same process.

The development of the synthetic dye industry is an example of a situation that often exists in industrial processes. The art precedes the science. An empirical method of carrying out a process may yield an acceptable product before scientific knowledge has advanced to the point where the actual chemical reactions are known and understood. Even today, one class of dyestuffs, the sulfur dyes, are widely used, but their exact chemical structures are uncertain.

We have said before that the development of color depends on the absorption of certain portions of visible light and the reflection of the remainder. It has been found that certain groupings must be present before compounds exhibit this phenomenon. These groups that cause the absorption of light in the visible range, and accordingly give color to the compound, are known as *chromophore groups.* Hence, a *chromophore group can be defined as any group of atoms that gives color to a* *compound.* A few of the more important chromophore groups occurring in dyes are:

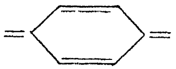
1. Nitro



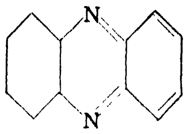
2. Azo

$-N{=}N-$

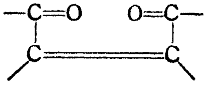
3. Quinoid



4. Azine



5. Indigoid



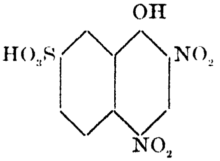
Not all colored compounds are dyes. The color must be capable of being permanently attached to a fiber, leather, or other solid material. In order for a substance to function as a dye, it must contain *auxochrome* groups. An auxochrome group enables the dye to be fixed to the solid material. The auxochrome groups can be divided into two classes: the basic groups and the acidic groups. The basic groups are the primary amino group, $-NH_2$, the secondary amino group, $-NHR$, and the tertiary amino group, $-NR_2$. They deepen and intensify the color. The acidic groups, such as the carboxyl group, the sulfonic acid group, and the hydroxyl group, usually do not intensify the color. It will be noted that all the auxochrome groups are salt-forming groups and are important in rendering the dye soluble.

Classification of the Dyes.—The chemistry of dyestuffs is extremely complex, and space will limit us to a brief treatment of the subject. There is a very extensive literature on the chemistry of dyestuffs, and this includes thousands of patents for their manufacture. For such an involved subject it is especially desirable to have a system of classification. There are two systems used for classifying dyes. The one that is of the most interest to the chemist is based on their chemical structure. The dye plant operator classifies dyes according to the method of application.

In the following classification (based on chemical structure), only a few of the more frequently used classes will be discussed.

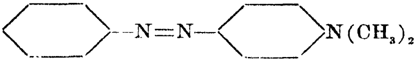
Nitro dyes. Picric acid is an example of this group. It gives a pure yellow color to wool and other protein compounds. It is not used widely now since it has been replaced by other dyes that give more desirable shades of yellow.

The disodium and the dipotassium salts of *naphthol-yellow-S* are used as yellow coloring for foods, drugs, and cosmetics. Naphthol-yellow-S also is used for dyeing wool and silk.



Naphthol-yellow-S
(2,4-dinitro-1-naphthol-7-sulfonic acid)

Azo dyes. This class of dyestuffs is synthesized by the coupling of a diazotized primary amine with an amine, phenol, or naphthol. There are more representatives of the azo type of dyes than of any other class of dyestuffs. One of these is *butter yellow,* which is prepared by coupling diazotized aniline with dimethylaniline.



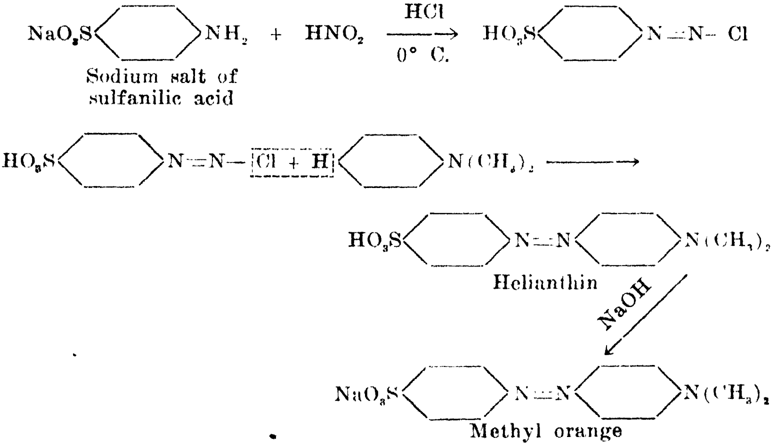
Butter yellow

This dye has been shown to produce cancer in experimental animals. Contrary to a widely held belief, this dye is not permitted to be used in foods, drugs, or cosmetics. Butter yellow is used sometimes as an indicator in the titration of gastric contents to determine the concentration of free hydrochloric acid.

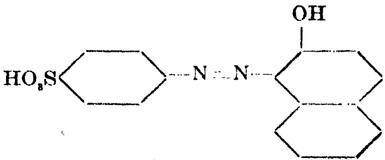
Bismarck brown is prepared by the diazotization of both of the amino groups of m-phenylenediamine, followed by coupling with two other molecules of the undiazotized compound. It imparts a dark brown color to silk and wool, and to cotton as well if a mordant is used. Both butter yellow and Bismarck brown are basic azo dyes.

Methyl orange is an example of an acidic azo dye. The preparation of methyl orange will be given in detail, since it is typical of the preparation of the azo dyes. Methyl orange is a valuable indicator for the titration of acids and bases, but it is not used ordinarily for dyeing fabrics.

For the preparation of methyl orange, or the sodium salt of 4-dimethylamino-azobenzene-4-sulfonic acid, sulfanilic acid is diazotized and coupled with dimethylaniline. As the procedure is carried out, the sulfanilic acid is dissolved in sodium carbonate solution, and the required quantity of sodium nitrite is added as a 10 per cent solution. This mixture is cooled to 0° C., and hydrochloric acid is added slowly with stirring. To this cold solution, dimethylaniline dissolved in hydrochloric acid is added. When the coupling reaction is completed, red crystals separate. This dye is known as helianthin. Its sodium salt, formed by the action of sodium hydroxide, is methyl orange.



β-Naphthol orange, also named *orange II,* is one of the very common dyes. In this case sulfanilic acid is diazotized and the product is coupled with β-naphthol. This dye is much used in acid solution to dye wool.



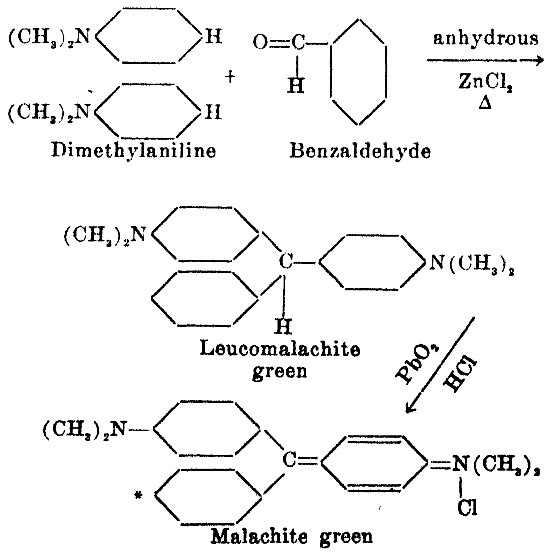
β-Naphthol orange
(orange II)

If α-naphthol is used instead of β-naphthol, orange I is formed. These orange dyes are acid azo dyes. Nearly always the sulfonic acid group, -SO_3H, is the acid group in the acid azo dyes.

There are a large number of other azo dyes, but the examples cited are typical of the class. By varying the groups in the compounds that are coupled, a number of dyes of different shades and hues can be prepared.

Triphenylmethane dyes. The dyes of this group are known as triphenylmethane dyes, because they are related in structure to triphenylmethane. Actually, however, they are not made directly from triphenylmethane.

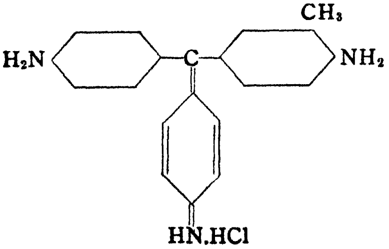
Malachite green is one of the simpler members of this class. It is synthesized by heating dimethylaniline with benzaldehyde in the presence of anhydrous zinc chloride. The resulting product is known as leucomalachite green. The prefix *leuco* is used to indicate that the compound is the colorless form of the dye. The leuco base is converted to the green dye by oxidation with lead dioxide in acid solution.



Malachite green dyes wool, silk, and leather a blue-green color. Cotton is dyed a deep, rich green, but a mordant, such as a combination of tannic acid and tartar emetic, is necessary. Malachite green is used also as a food dye.

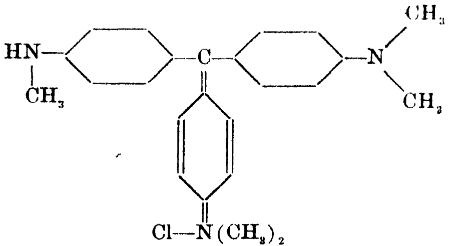
Gentian violet is the most extensively used of the triphenylmethane dyes. Its chemical structure is identical with malachite green except that a $(CH_3)_2N$ group is added at the point of the asterisk in the foregoing formula. It has a low toxicity and penetrates tissues readily. It is used against staphylococcus infections (boils), as an antiseptic for infected wounds, as a vermifuge, and in the treatment of certain infections of mucous membranes.

Fuchsine, or magenta, was one of the first triphenylmethane dyes to be synthesized. Fuchsine was given its name because its color resembles that of the petals of fuchsia. The French named it magenta after the battle of that name. It dissolves in water to give a deep red color. A solution of fuchsine dyes silk and wool directly but with cotton it is necessary to use a mordant, such as tannin or potassium hydrogen tartrate. Fuchsine is not widely used as a dye for textiles, because the red colors obtained are not fast to light. Fuchsine is used chiefly for the preparation of other dyes, such as aniline blue, that are closely related to it in structure. Some bacterial stains contain fuchsine. It will be remembered that a solution of fuchsine decolorized with sulfur dioxide is used as a reagent to test for the presence of aldehydes.



Fuchsine

Methyl violet also belongs to the triphenylmethane class of dyes. It is prepared by oxidizing dimethylaniline with copper sulfate in the presence of phenol. The structural formula assigned to this dye is:

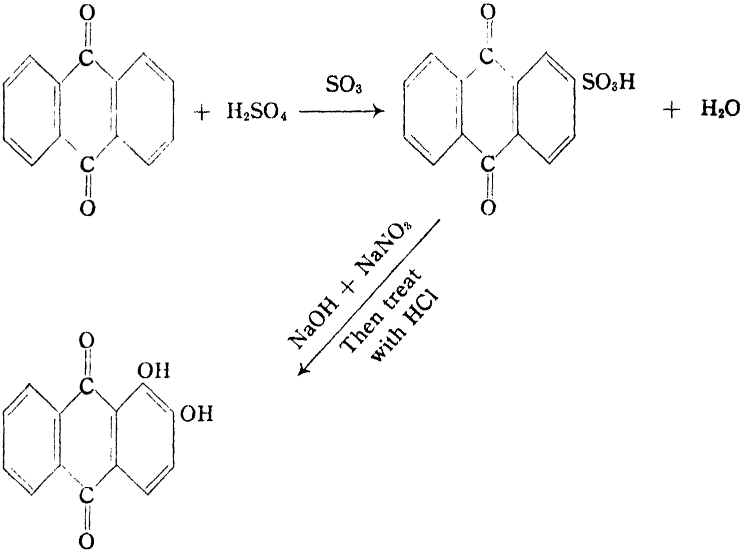


Methyl violet

The student should note the similarity in structure between methyl violet and fuchsine. Methyl violet, which is pentamethyl parafuchsine, gives a violet solution, whereas a solution of fuchsine is deep red. If the methyl groups in methyl violet are replaced by phenyl or naphthyl groups, the dye has a pure blue color in solution. A particular example of the substitution of phenyl groups is triphenyl parafuchsine (aniline blue), which has practically no red hue. Hence it can be seen that changes in the groups attached to the same nucleus will change the color of the dye. Smaller changes in the structure of a dye may give different shades of the same color.

Methyl violet dyes wool and silk directly, and dyes cotton that has been mordanted with tannic acid and tartar emetic. The dye is used in the manufacture of indelible inks, inks for stamp pads, lithographic inks, carbon paper, typewriter ribbons, and as an indicator.

Anthraquinone dyes. The most familiar member of this group is *alizarin.* It is found as the glucoside, ruberythric acid, in the root of madder, a shrub formerly widely cultivated in France. The Persians, Egyptians, and Hindus prepared this dye from madder root in ancient times. The development of the synthetic dye, manufactured by the process developed by Graebe and Liebermann, and by Perkin, soon drove the natural product from the market. The starting material for the manufacture of alizarin is anthraquinone. This is sulfonated at 160° C. to give the β-sulfonic acid derivative.



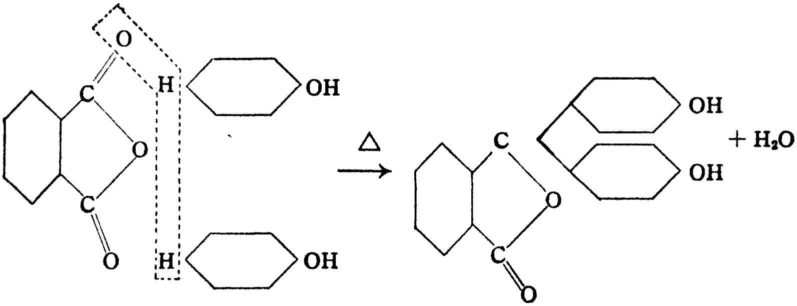
Alizarin

Alizarin is obtained by heating the sulfonic acid in an autoclave with sodium hydroxide and an oxidizing agent, such as sodium nitrate or sodium chlorate. This treatment replaces the sulfonic acid group with the hydroxyl group, and oxidizes the alpha hydrogen of the benzene nucleus to an hydroxyl group. The process yields the sodium salt of the dye, from which the free dye can be obtained by the addition of a strong acid.

Alizarin is only slightly soluble in water, but it dissolves readily in alkalies and in alcohol. It is a typical mordant dye, and special treatment of the fabric to be dyed is necessary to obtain satisfactory results. In spite of these requirements for its successful use, alizarin was used in ancient times. In the dyeing of cotton, the fabric or yarn is impregnated with *Turkey red oil,* which is made by treating castor oil with concentrated sulfuric acid, followed by neutralization of the resulting product. After this treatment the cotton is dried and placed in a bath of aluminum sulfate or acetate. This results in the formation of aluminum salts of the sulfated fatty acids in the castor oil. In order to make these salts completely insoluble, the fabric is drawn through a vat containing chalk. The dyeing process is completed by passing the fabric through a bath of alizarin to which some tannin has been added. In this way the brilliant red color, known as Turkey red, is obtained. The color thus produced is especially fast to light and laundering, which accounts for the commercial value of alizarin as a dye.

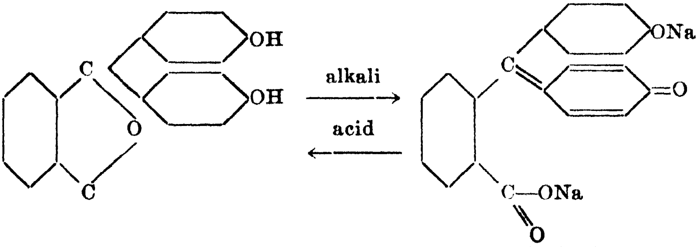
Aluminum mordants usually are used with alizarin, but other metals can be employed. When iron compounds are used as mordants, various violet colors are obtained. With chromium salts brownish-red tones result. In dyeing wool and silk with alizarin, metallic mordants also are used.

Phthalein dyes. The phthalein dyes are made by a reaction between phthalic anhydride and a phenol. Phenolphthalein is a prominent member of this group. It is synthesized by heating phthalic anhydride and phenol. The hydrogens para to the hydroxy groups in the two phenol molecules split out water with the oxygen of one of the carbonyl groups of the phthalic anhydride.



Phthalic anhydride Phenol Phenolphthalein

The resulting compound is a white crystalline solid that is soluble in alcohol, but almost insoluble in water. When this compound, known as the acid form, is treated with a base, a rearrangement takes place in which a quinoid structure is formed. The resulting salt has a bright purplish-red color. The addition of acid reverses the reaction, and the colorless form is obtained again.

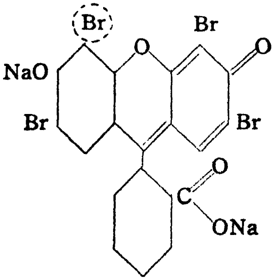


Colorless form
(in acid)

Red quinoid form
(in NaOH)

Phenolphthalein undergoes this molecular rearrangement with only a slight change in hydrogen and hydroxyl-ion concentration, and it is widely used as an indicator for the titration of acids and bases. This color change of phenolphthalein is an illustration of the theory of indicators; that is, the color change of an indicator is due to changes in structure. The colorless lactone form results on acidification, while in alkaline solution the lactone ring immediately opens and a salt forms. The salt possesses a quinoid structure and is the colored form. This change in structure takes place very rapidly, and within a change of hydrogen-ion concentration of two pH units. A number of organic compounds possess different structures and colors at different hydrogen-ion concentrations, but unless this change takes place rapidly and over a small range of pH, the substance cannot be used as an indicator.

Phenolphthalein is not used as a dye. It is the active component in many laxatives, such as Feen-a-mint, Ex-lax, Phenolax, etc.



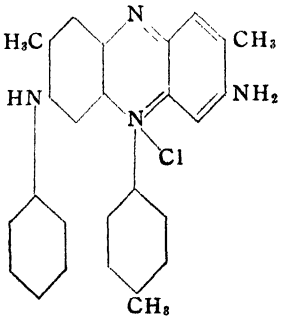
Eosin

By heating resorcinol with phthalic anhydride in the presence of anhydrous zinc chloride, a dye known as fluorescein is obtained. This dye has a brilliant yellowish-green fluorescence. It has a remarkably high tinctorial power, and, because of this property, fluorescein was used to locate leaks in the pipe line laid under the English channel to supply the Allies in Normandy with gasoline and other petroleum products during World War II.

The sodium or potassium salt of tetrabromofluorescein is *eosin,* an important dye. Eosin derives its name from the Greek word for dawn, the color of the dye resembling the color of the sky at dawn. Eosin is used to dye silk and wool a fluorescent rose color. It is used also for dyeing paper, in the manufacture of red ink, and for staining biological material.

Mercurochrome, an antiseptic, is a mercury derivative of eosin in which one of the bromine atoms (circled by broken lines in the foregoing formula) is replaced by an hydroxy mercury group, -HgOH.

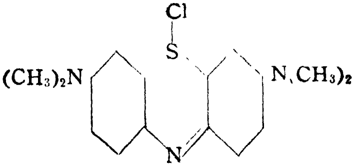
Azine dyes. These dyes also are called phenazine dyes or phenylphenazonium dyes. They usually have a high molecular weight, and the intermediate steps in their preparation are involved and somewhat obscure. *Mauve,* or mauveine, is a member of this class of dyes. It has been mentioned already as the first synthetic dye discovered by Perkin, and the one that led to the rapid development of the synthesis of other dyes. The result obtained by Perkin was due to the toluidines that were present as impurities in the aniline. Later, mauve was manufactured by the oxidation of a mixture of aniline and the toluidines with dichromate in acid solution. Its structure can be represented as follows:



Mauve
(Mauveine)

Safranine and *aniline black* are two other members of this group. Some idea of the size of the molecule of aniline black can be gained from the fact that it contains eleven aniline residues joined in such a manner that there are three azine groups, in addition to primary and secondary amino groups.

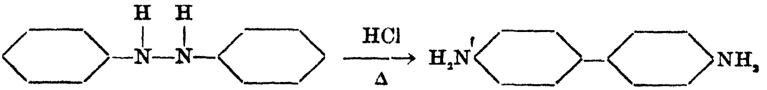
Methylene blue is a *thiazine dye,* so named because a sulfur atom has replaced nitrogen in the azine nucleus. It is prepared from dimethyl-p-phenylenediamine, dimethylaniline, and sodium thiosulfate. Upon the oxidation of the product obtained by the reaction of these substances, methylene blue is formed.



Methylene blue

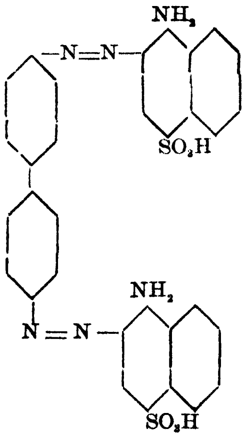
Methylene blue is used extensively in dyeing cotton that has been mordanted with tannic acid. It does not dye wool readily, but is used for silk. Methylene blue is much used as a stain for bacteria, nerve tissue, and other biological material.

Classification of the Dyes According to Their Method of Application.—*Direct or substantive dyes.* Wool and silk are dyed directly by a large number of dyes. This is possible since wool and silk both are protein materials and contain amino and carboxyl groups in their structure. These groups can form salts with the acid or basic dyes. Cotton and the rayons, except cellulose acetate, contain free hydroxyl groups that are weakly acidic and are unable to form salts with the dyes. For some reason, as yet unknown, one class of dyestuffs, the members of which are derivatives of benzidine, will dye cotton directly. Benzidine is made from hydrazobenzene. When hydrazobenzene is treated with concentrated mineral acid, an unusual rearrangement takes place. It is almost like turning the molecule inside out.



Hydrazobenzene   Benzidine

Both of the amino groups in benzidine can be diazotized. The process is known as tetrazotization. The tetrazotized compound, like the ordinary diazotized compounds, can be coupled with amino compounds or phenolic substances. Congo red is a typical benzidine dye. In its preparation benzidine is tetrazotized and coupled with naphthionic acid.



Congo red

Congo red is used as an indicator. It is one of the simplest members of the direct dyes.

The dyes that are sold for use in the home almost without exception are direct dyes that can be used directly for cotton as well as for wool and silk.

Adjective or mordant dyes. As was mentioned earlier, there are only a few direct cotton dyes. In order to use other dyes, it is necessary to treat the cloth with a substance known as a mordant, which will unite with the fiber on one hand and with the dye on the other. There are two types of mordants, the basic and the acidic. The basic mordants are used with acid dyes such as alizarin. For the application of this type of dye, the cloth or yarn is soaked in solutions of easily hydrolyzable salts. The salts commonly employed are the iron, aluminum, and chromium salts of the organic acids. After the textile material is soaked in one of these solutions, it is treated with steam, which converts the salt to the hydroxide or basic salt. The basic material thus formed is in a finely divided or colloidal state, and becomes firmly attached to the fiber. The mordanted fiber now is passed into a solution of the dye, which can combine with the metallic salt to form the complex, insoluble colored compound known as a *lake.* This color lake remains firmly attached to the fiber, and the dye is said to be "fast."

If a basic dye is to be used, an acid mordant first must be applied to the cotton fiber. This is accomplished by treating the fiber or material with tannic acid, which then is fixed in an insoluble form by treatment with tartar emetic. Antimony tannate thus is precipitated on the fiber. The fiber and the dye have opposite electrical charges; thus the dye is attracted to the fiber and an insoluble compound is formed.

When basic mordants are used, the ionization of the hydroxyl group leaves a positive charge on the fiber. The colloidal dye having a negative charge thus is attracted to the fiber. Mordants are used mainly in the dyeing of cotton.

Ingrain or developed dyes. The dyes of this group are applied to cotton by forming the dye in the textile fiber. The formation of para red will be used as an example of this type of dye. The yarn or cloth first is soaked in an alkaline solution of β-naphthol, after which it is passed through a solution of diazotized p-nitroaniline. A bright red dye is developed directly in the fibers. The reverse process, in which the cloth is treated with a dye containing a primary amino group, also can be used. The textile material then is passed through a cold dilute solution of nitrous acid, which diazotizes the amino group of the dye. The cloth next is passed into an alkaline solution of an amine or a phenol, and coupling takes place to form the dye in the fiber. Dyes produced in this manner are very fast and are much used on cotton materials.

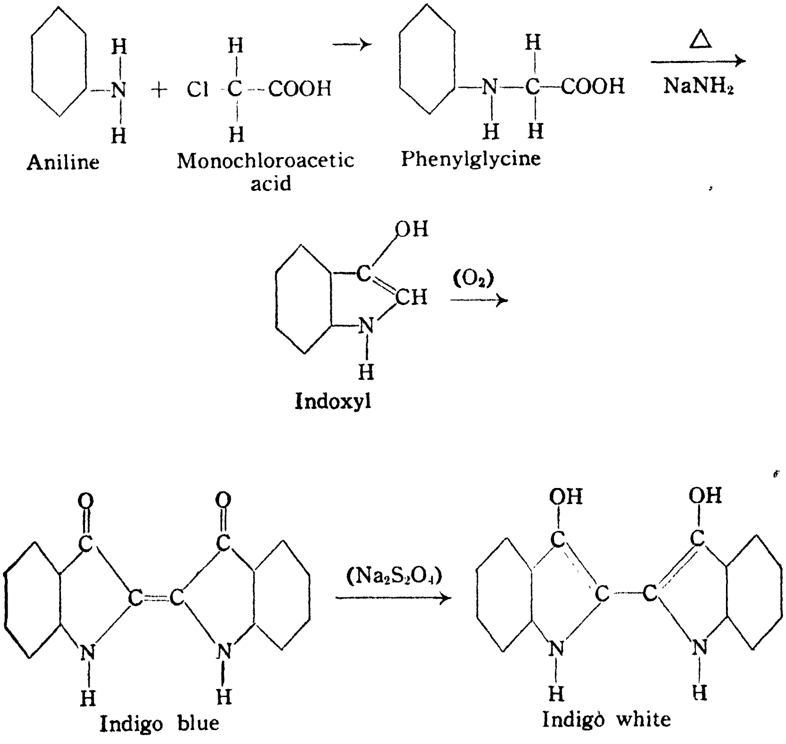
Vat dyes. Vat dyes are insoluble in water and in dilute acids and alkalies. In order for the dyes to be applied to a fabric, they must be reduced to phenolic compounds, which will form soluble salts. The reduced compounds, termed leuco bases, usually are colorless, or very much lighter in color than the dye. The fabric that has been impregnated with the leuco base is dried in air.

During the drying, the dye is oxidized back to the very insoluble form. The members of this class of dyes are known as vat dyes, since the reduction to the soluble form often is done in large vats. Vat dyes are used widely, because they are fast to washing, and are very stable to the effects of light. Another advantage of the vat dyes is that they can be used on both vegetable and animal fibers without a mordant.

Indigo is by far the most important of the vat dyes. It has been estimated that over a thousand different dyes are produced commercially, but indigo leads them all in the quantity produced. It was one of the dyes known to the ancients. It was used as early as 1600 B.C. Mummies of the Eighteenth Dynasty have been found in wrappings dyed with indigo. Indigo was obtained from species of *Indigofera,* which were native to tropical countries. The indigo is present in these plants as the glucoside, indican. The macerated indigo plants were placed in large vats where they were allowed to ferment. The colorless form of indigo was liberated by an enzyme during the fermentation. Vigorous stirring of the mass oxidized the colorless form to indigo, which rose to the top of the tanks as a blue scum. In 1897 there were about one million acres devoted to the growing of indigo plants. The crop had an annual value of about $20,000,000. By 1914 the value of the crop had dropped to $300,000. The reason for this decrease was the commercial production of synthetic indigo.

The brilliant researches of Adolf von Baeyer and his collaborators first established the structure of indigo. It soon was discovered that indoxyl gives indigo when it is oxidized, so that the manufacture of the dye was dependent on a commercially feasible method for synthesizing indoxyl. Baeyer was the first to synthesize indigo, but his synthesis is not practical as an industrial method. He devised two later methods for the synthesis of indigo, both of which were used for a time for the industrial production of the dye, but they failed to be profitable.

There are several methods in use at the present time for the production of indigo. The one that we shall describe is due mainly to the work of Heumann. This method was selected since it is the simplest and serves to illustrate the structure of indoxyl. In this synthesis, aniline is the starting material. Aniline is made to react with monochloroacetic acid to yield phenylglycine. This product is fused with alkali in the presence of soda amide to give indoxyl. The method was not successful until the discovery of soda amide as a condensing agent. Without soda amide the temperature required was very high, and the yields were low. The mass resulting from the fusion is diluted with water, and air is blown through the alkaline mixture. The indigo that is formed precipitates and is washed on a filter. The steps in this synthesis are shown by the following equations.



Indigo is reduced to indigo white with sodium hyposulfite ($Na_2S_2O_4$), often called sodium hydrosulfite or sodium bithionate. The fiber is immersed in the leuco base until it is thoroughly impregnated with the dye. On exposure to air indigo white is oxidized to the very insoluble indigo blue, which is fixed firmly to the fiber.

Considerable quantities of indigo also are used for the preparation of derivatives. One derivative, 6,6′-dibromoindigo, has been shown to be the same as Tyrian purple, the dye used by the ancients to secure the royal purple color. It was obtained in ancient times from a snail-like shellfish, *Murex brandaris,* which was abundant in the water of the Mediterranean near Tyre. The Phoenician merchants, who knew how to extract the dye from the mollusks, made their fortunes from it. In modern times the chemical structure of Tyrian purple was established by an investigation of the substance obtained from the shellfish. Over 1,200 specimens yielded only 1.4 grams of the pure substance. Careful analysis and chemical reactions demonstrated that the substance was 6,6′-dibromoindigo. This substance, which was so highly prized over 2,000 years ago, is not manufactured now, for similar colors can be produced more cheaply from other derivatives of indigo.

Study Questions

1. How is aniline prepared commercially?
2. What are several uses of acetanilide? Write the formula for this compound.
3. What is the formula for sulfanilamide? Outline briefly the important steps in the discovery of the effectiveness of this drug.
4. Name four or five derivatives of sulfanilamide and state what diseases they have been most successful in combating.
5. What is the name of the product resulting from the oxidation of aniline by sulfuric acid and sodium dichromate?
6. In what respects does vulcanized rubber differ from the raw rubber? What role do "accelerators" play in the vulcanization process? Name several of these materials.
7. What is the function of a "booster" in military explosives? Name a compound that is employed for this purpose.
8. What are the toluidines? The xylidines? Write formulas of compounds belonging to these two classes.
9. In what respect is the phenylene radical similar to the methylene radical?
10. What are the physiological effects of benzedrine sulfate? Why is it dangerous for students to use this drug indiscriminately?

11. Compare the reaction of primary aromatic amines and nitrous acid with the same acid and primary aliphatic amines. Why must diazotization reactions be carried out at a low temperature?
12. How does the reaction of tertiary amines with nitrous acid differ from the reaction of tertiary aliphatic amines with the same acid?
13. Write the equation for the preparation of benzenediazonium chloride from aniline hydrochloride. In what respects do the diazonium salts resemble the ammonium or quaternary ammonium salts?
14. Cite examples of some of the replacement reactions that diazonium compounds undergo.
15. Starting with benzene, write a series of equations for the synthesis of m-dichlorobenzene.
16. Write formulas for the two tautomeric forms of benzenediazonium hydroxide.
17. What type of nitrogen linkage is involved in coupling reactions? What is the valence of nitrogen in such reactions?
18. Write the equation for the coupling of benzenediazo chloride with aniline.
19. Name three aminophenols that are used as photographic developers. Explain the process involved in the formation of a photographic film.
20. What is a working definition of dyes?
21. Describe the synthesis of the first dye.
22. What is a chromophore group? A color lake? An auxochrome group? List examples of typical chromophore groups.
23. What are two possible methods of classifying dyes?
24. List at least one member of each of the following classes of dyes and designate the chromophore group in each instance: Nitro dyes, azo dyes, triphenylmethane dyes, anthraquinone dyes, phthalein dyes, and azine dyes.
25. Describe the dyeing of cotton with Turkey red.
26. What characteristics must a dye possess before it becomes useful as an indicator?
27. Why are wool and silk fabrics dyed more easily with direct dyes than are cotton or rayon fabrics?
28. What mordants commonly are used with acid dyes? With basic dyes?
29. What is meant by the term *leuco base?*
30. How are ingrain dyes applied to textile materials?
31. What is an example of a vat dye? Describe the process of vat dyeing.
32. Write equations for the synthesis of indigo.

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CHAPTER XIX

HETEROCYCLIC COMPOUNDS

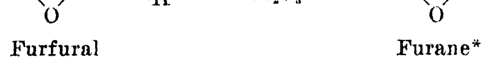
Introduction.—Most of the cyclic compounds studied thus far have contained only carbon atoms in the ring. These compounds often are called *homo*cyclic or *carbo*cyclic compounds. The class of compounds to be considered now contain atoms other than carbon in the ring structure, and are termed *heterocyclic* compounds. The prefix *hetero* is derived from the Greek word meaning other or different.

The lactones and the anhydrides of the acids could be considered as heterocyclic compounds. However, they are considered usually with the aliphatic or open-chain compounds to which they are related, since they are easily formed from, or converted to, these compounds. Another reason for considering the lactones and the anhydrides with the aliphatic compounds is that they are comparatively reactive, the ring structure being broken easily by hydrolysis; whereas the heterocyclic compounds to be considered now, resemble the aromatic compounds in that their ring structure is very stable.

In the more common heterocyclic compounds the hetero atom is oxygen, sulfur, or nitrogen. In some cases phosphorus or selenium may act as the noncarbon atom in forming the ring. The more important heterocyclic compounds contain five- or six-membered rings, or contain these rings condensed with a benzene ring.

Heterocyclic Compounds With Five-Membered Rings

Furane.—The heterocyclic compound containing oxygen and four carbon atoms in the ring is known as furane. It is



Furfural Furane*

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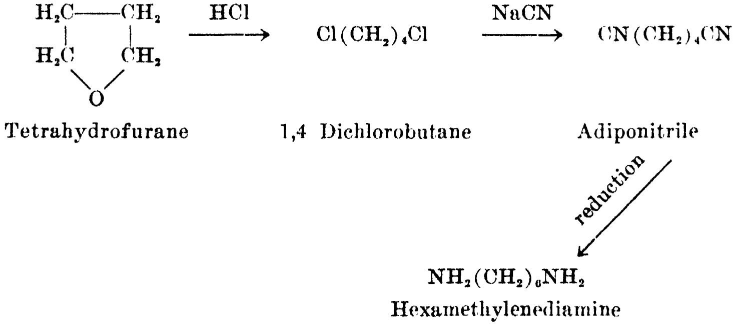
*The system of writing the heterocyclic formulas in this chapter will be to place the hetero atom at the bottom. This is a widely used practice at the present time, although, in some textbooks and literature, this position is reversed, and the hetero atom is written at the top or even to the side.

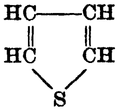
obtained commercially by the oxidation of furfural to furoic acid and the decarboxylation of this compound to form furane. The furane then can be reduced in the presence of a nickel catalyst to tetrahydrofurane. This cyclic ether is an excellent solvent for use in Grignard reactions. On treatment with concentrated hydrochloric acid in the presence of zinc chloride, tetrahydrofurane yields 1,4-dichlorobutane. This compound, if treated with sodium cyanide and the product reduced, forms hexamethylenediamine. This diamine when condensed with adipic acid and polymerized yields one type of nylon. The series of reactions involved can be illustrated as follows:



Since furfural can be obtained from corncobs, these equations give the basis for the report that nylon may be made from corncobs.

The formation of furfural by heating pentoses with 12 per cent hydrochloric acid already has been discussed (see page 318).

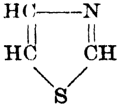
Thiophene.—The sulfur analogue of furane is a compound called thiophene. It occurs along with benzene in coal tar. The boiling point of thiophene is 84° C., whereas that of benzene is 80.4° C.; hence it is difficult to separate the two compounds by fractional distillation, and commercial benzene always contains traces of thiophene. The separation of thiophene from benzene depends upon the fact that thiophene sulfonates more readily than does benzene. When crude benzene is shaken with concentrated sulfuric acid, thiophene sulfonic acid is formed, and dissolves in the sulfuric acid layer.



Thiophene

In its chemical reactions thiophene resembles the aromatic compounds much more closely than it does the aliphatic compounds. The aromatic character of thiophene is shown by the fact that chlorination results in substitution, rather than in addition, and monochloro-, dichloro-, and tetrachloro- derivatives are formed. The nitration of thiophene is more difficult than the nitration of benzene.

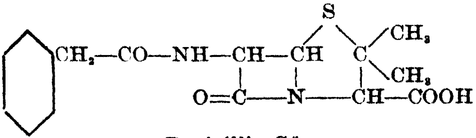
Thiazole.—A heterocyclic compound containing both nitrogen and sulfur in a 5-membered ring is thiazole. Both sulfathiazole and vitamin B_1 (see page 710) contain the thiazole ring in their structure.



Thiazole

Penicillin is another compound containing a thiazole ring. The discovery of penicillin was the most spectacular step in modern medicine since the development of the sulfa drugs. Penicillin has proved its effectiveness against a number of diseases that do not yield to sulfa therapy. In addition, penicillin has the important advantage over the sulfa drugs in that it is not frequently attended by toxic symptoms.

Penicillin-G, or benzylpenicillin, at present is the most widely used of the various types of known penicillins. The synthesis on a microscopic scale of this compound was announced in 1946. Its structural formula is thought to be:



Penicillin-G*

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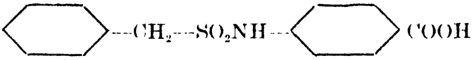
*Commercial products are usually the salts of this compound. The free acid is quite unstable.

The structures of the other types of penicillin, such as penicillin X, K, and F, differ in the groups attached to the heterocyclic nucleus. Some have been shown to have greater medical effectiveness than penicillin-G, but in most cases their increased cost more than offsets their usefulness.

The recent announcement of the development of procaine penicillin (a combination of procaine with a penicillin) in a mixture of aluminum stearate and oil helps to solve one of the most vexing problems of penicillin therapy—that of maintaining a satisfactory blood level of the compound over an extended period of time. Because the ordinary forms of penicillin are so soluble, they are rapidly excreted by the kidneys. A few years ago, when the drug was rare and very expensive, it often was recovered from the urine of patients receiving it. Procaine penicillin is sparingly soluble so that higher blood levels can be maintained over a much longer period of time with smaller and less frequent doses of the antibiotic.

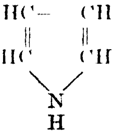
Other means have been used for combating this difficulty in penicillin therapy. The drug has been administered in beeswax and oil vehicles with some success, but local reactions are apt to occur because of the wax. The simultaneous administration of the drug caronamide has been found effective in enhancing blood levels of penicillin. This drug, which has the following formula, suppresses the excretion of penicillin by the renal tubules and thus acts to increase effectively the blood level of penicillin.



Caronamide (Staticin)

Originally, sodium penicillin was available commercially only in an amorphous state, which is relatively unstable unless refrigerated. Most of the drug on the market now is in the more stable crystalline form. The exact methods for crystallization are commercial processes that have not been revealed. About 75 per cent of the potency of amorphous penicillin is lost in eight days at a temperature of 60° C. On the other hand, under the same conditions crystalline penicillin loses only 3 per cent of its activity.

Pyrrole.—The five-membered heterocyclic ring containing one nitrogen atom is known as pyrrole.



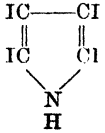
Pyrrole

This nitrogen analogue of furane and thiophene occurs to a slight extent in coal tar, and more abundantly in bone oil (Dippel's oil), which is obtained by the distillation of bones from which the fat has not been removed. The residue is used for the preparation of bone charcoal.

Pyrrole is important since many natural products are complex derivatives of it. Important biological substances that contain pyrrole rings in their structure are hemoglobin, the coloring matter of blood; chlorophyll, the green pigment of plants; and bilirubin, the principal pigment of bile.

Pyrrole is a colorless liquid that turns brown on standing. It boils at 131° C., and is only slightly soluble in water; however, it is soluble in alcohol and ether. If a pine wood splint moistened in hydrochloric acid is held in the vapors of pyrrole, a fiery red color is formed. This is a characteristic reaction of pyrrole, and is used for detecting the presence of the compound in unknown solutions. The word *pyrrole* is derived from Greek and Latin words meaning "fiery red."

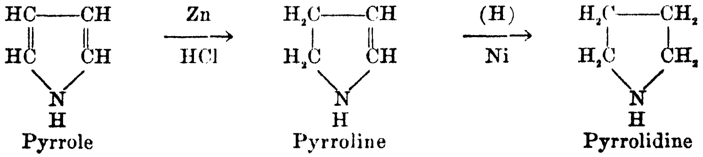
Chemically, pyrrole resembles the aromatic compounds. Although the formula is written with ethylenic double bonds, pyrrole reacts with halogens to form substitution products. The tetraiodo substitution product is known as iodol.



Iodol

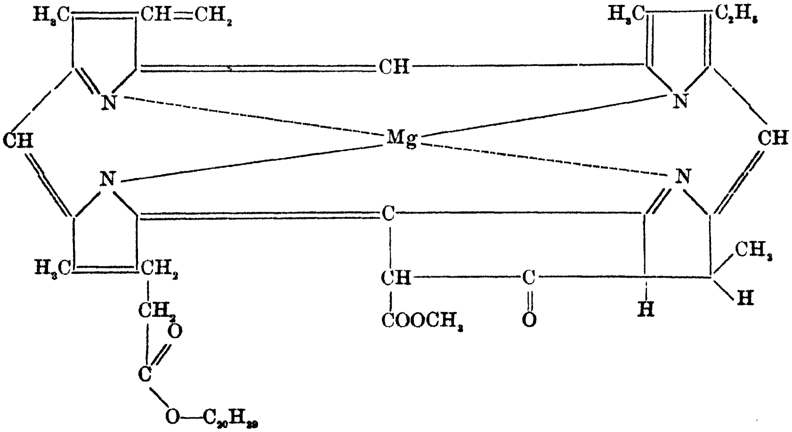
Iodol resembles iodoform in its reactions, but it is odorless and nonirritating.

Pyrrole is very sensitive toward mineral acids, forming polymerization products. It can be reduced by the action of zinc and hydrochloric acid to pyrroline, in which one of the double bonds has been reduced. This compound can be hydrogenated further to the saturated compound, pyrrolidine, by the action of hydrogen in the presence of nickel.



The alkaloid, nicotine, and the amino acids, proline and hydroxyproline, are derivatives of pyrrolidine.

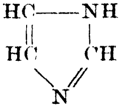
Chlorophyll.—Chlorophyll is the organic catalyst in photosynthesis, the reaction by means of which plants in the presence of radiant energy are able to synthesize sugars from carbon dioxide and water. Our knowledge of the structure of chlorophyll is due to a number of investigators, prominent among whom are Conant, Willstätter, Stoll, and Hans Fischer. The structure of *chlorophyll a* proposed by H. Fischer is:



Chlorophyll a

A comparison of this formula with the structure assigned to the prosthetic group of hemoglobin (see page 590) will show striking similarities. (The functions of hemoglobin are discussed in Chapter XXIII.) Reference to the structural formula of bilirubin (page 657) will show the presence of the same nucleus of four substituted pyrrole rings.

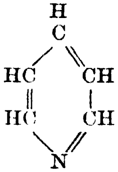
Imidazole.—Another heterocyclic compound containing a 5-membered ring is imidazole. Histidine and histamine (see pages 555 and 646) contain this heterocyclic structure in their formula.

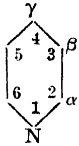


Imidazole

Heterocyclic Compounds With Six-Membered Rings

Pyridine, C_5H_5N.—Pyridine can be thought of as benzene in which a CH group has been replaced by a nitrogen atom.





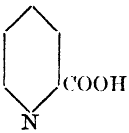
The numbering and the positions in the rings are indicated by the numbers and letters. This heterocyclic nitrogen compound occurs in the light oil fraction of coal tar. It has been estimated that from 100,000 to 200,000 gallons of pyridine are available from the amount of coal tar distilled annually in the United States. It also occurs in California petroleum, in Dippel's oil, and in small amounts in tobacco smoke.

Pyridine is a colorless liquid when it is pure. It boils at 115° C., and is soluble in both water and organic solvents. It has a characteristic putrid, nauseating odor, which explains its use in denaturing alcohol.

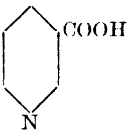
Chemical Properties of Pyridine.—The most characteristic chemical property of pyridine is its stability. It is unaffected by chromic acid (H_2SO_4 + $Na_2Cr_2O_7$), boiling nitric acid, or potassium permanganate. This explains why oxidation of organic compounds with potassium permanganate often is carried out in pyridine; it is a solvent for many organic compounds and is stable in the presence of the oxidizing agent. The stability of pyridine explains its presence as one of the decomposition products when many nitrogenous compounds are subjected to destructive distillation, oxidation, or other decomposition reactions.

The aromatic character of pyridine is illustrated by the formation of sulfonic acid derivatives and halogen substitution products, but sulfonation only takes place at about 300° C., and halogen-substituted products are formed with difficulty. Under ordinary conditions, nitration does not take place.

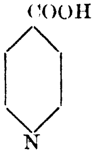
Alkyl side chains on the pyridine ring can be oxidized to carboxyl groups. This is similar to the behavior of the alkyl derivatives of benzene. The methyl derivatives of pyridine are known as picolines. On oxidation, they yield the following pyridine-monocarboxylic acids:



Picolinic acid



Nicotinic acid

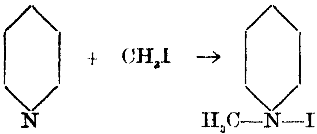


Isonicotinic acid

The pyridine-carboxylic acids often occur among the degradation products of alkaloids, and their identification is important in determining the structure of the alkaloids. Nicotinic acid, 3-pyridine-carboxylic acid, is the PP-factor (pellagra-preventing factor) in the vitamin B complex (see page 709). Another vitamin that is related in structure to pyridine is pyridoxine (vitamin B_6) (see page 715).

Uses of Pyridine.—Pyridine protects metals against acid corrosion. The property is utilized in its application as an inhibitor in the "pickling" of metals preparatory to galvanizing, and in the treatment of casings in oil wells before the introduction of acid for the purpose of releasing additional oil from the oil-bearing strata. Pyridine is the starting point for a number of chemical syntheses since it is available from coal-tar products.

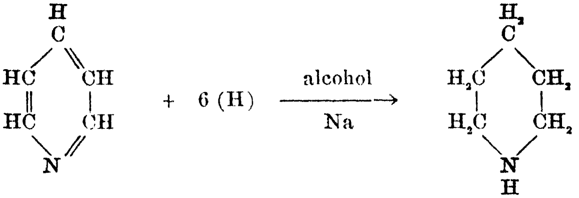
Pyridine Derivatives.—Pyridine is a tertiary amine and forms stable salts. It also reacts with alkyl halides to form quaternary compounds known as *pyridinium derivatives.* The higher alkylpyridinium salts, such as cetylpyridinium chloride, are being used as antiseptics.



Pyridine Methyl pyridinium iodide

On reduction with sodium and alcohol, pyridine combines with six atoms of hydrogen to form piperidine.

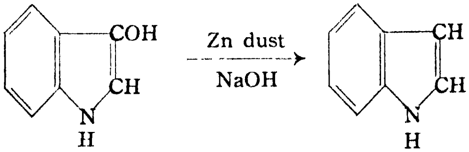
Piperidine was obtained first as a decomposition product of piperine, the alkaloid in pepper, from whence it obtained its name. The piperidine nucleus is present in coniine, the simplest alkaloid (see page 529). Piperidine is a colorless liquid possessing an ammoniacal odor. It is miscible with water, alcohol, ether, and benzene. In contrast to pyridine, which is a weak tertiary amine with aromatic properties, piperidine is a strong secondary amine, and resembles the secondary aliphatic amines in character. It is used as an accelerator in the vulcanization of rubber.



Pyridine Piperidine

Heterocyclic Compounds With Condensed Rings

Indole.—The heterocyclic compound whose formula corresponds to a fusion of a benzene ring with pyrrole is known as *indole.* Indole (benzopyrrole) commonly is prepared by the reduction of indoxyl with zinc dust and alkali. It will be recalled that indoxyl, which is 3-hydroxyindole, is the compound that yields indigo blue on oxidation. Due to the importance of this dye, large quantities of indoxyl are available commercially.

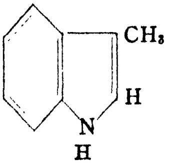


Indoxyl Indole

Indole is formed in the intestinal tract as a result of bacterial putrefaction of undigested protein material, and is present in feces. When it is absorbed from the intestinal tract, it is detoxified in the liver and is excreted as urinary indican (formula, page 647). It also occurs in jasmine flower oil to the extent of 2.5 per cent. In addition, oil of orange blossoms and other flower oils contain small amounts of indole. It is a crystalline solid, melting at 52° C. As ordinarily obtained, it possesses an unpleasant fecal odor. Strangely enough, when it is carefully purified and mixed in the desired dilution with other perfumes, the odor of fresh flowers is imparted to the mixture.

Indole resembles pyrrole in its weakly basic properties, and it forms resins with acids. It also gives a bright red color when a pine splint moistened with hydrochloric acid is held in its vapors.

Derivatives of indole are very widely distributed in nature. *Skatole,* β-methylindole, is produced by the putrefaction of unabsorbed protein material in the intestines and is present in human feces.

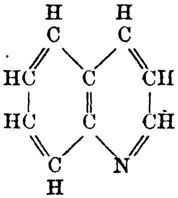


Skatole

It is derived from the amino acid, tryptophan, a constituent of proteins. Skatole is a solid that melts at 95° C. It has a powerful, repugnant odor.

Another derivative of indole is heteroauxin (indole-3-acetic acid), one of the plant growth hormones (see page 705). It is used commercially for inducing root growth on plant cuttings. Heteroauxin occurs in urine. Other derivatives of indole-acetic acid also have been found effective as growth substances.

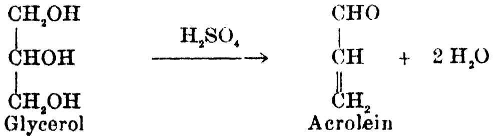
Quinoline (Benzopyridine).—From a structural viewpoint, quinoline represents the fusion of pyridine with a benzene ring, the union being in the α-β-positions of the pyridine.



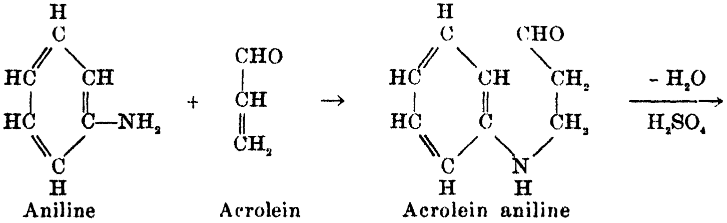
Quinoline

Quinoline also can be considered as naphthalene in which a CH group in the α-positions has been replaced by a N atom.

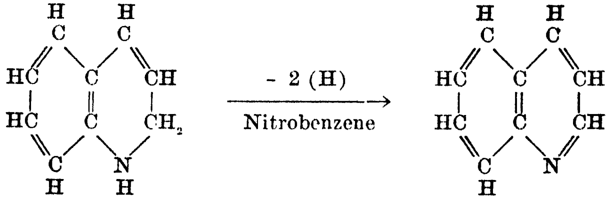
Quinoline occurs in coal tar and bone oil. Usually it is prepared by the Skraup synthesis. This consists of heating a mixture of aniline, glycerol, and nitrobenzene with concentrated sulfuric acid. The postulated steps of the reaction in the synthesis are: (1) the dehydration of the glycerol to form acrolein, (2) the condensation of the acrolein with aniline to form acrolein aniline; and (3) the dehydration of this addition compound by nitrobenzene to yield quinoline.

(1) 

$$\underset{\text{Glycerol}}{CH_2OH\text{—}CHOH\text{—}CH_2OH} \xrightarrow{H_2SO_4} \underset{\text{Acrolein}}{CHO\text{—}CH{=}CH_2} + 2\,H_2O$$

(2) 

(3)

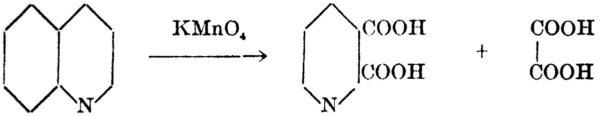


Dihydroquinoline Quinoline

This method also has been very useful in preparing derivatives of quinoline. Homologues of aniline, halogen- and nitrogen-substitution products of aniline, as well as aminophenols, can be substituted for aniline in the Skraup synthesis. The quinoline substitution products prepared in this way contain the additional groups in the benzene ring rather than in the pyridine ring part of quinoline. If naphthylamines are used instead of aniline, naphthoquinolines are obtained.

Quinoline is important since the antimalarials, quinine and plasmochin (see page 535), and the alkaloid, cinchonine, are derivatives of this heterocyclic compound.

Quinoline is a colorless, oily liquid. It is almost insoluble in water, but is soluble in alcohol and most other organic solvents. It is similar to pyridine in its chemical properties. Like pyridine, it is a tertiary base that forms salts with acids and quaternary compounds with alkyl halides. A marked difference between quinoline and pyridine is the behavior of the latter on oxidation. When quinoline is oxidized with potassium permanganate, pyridine-α-β-dicarboxylic acid (quinolinic acid) is obtained.

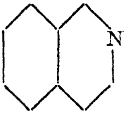


Quinoline Quinolinic acid Oxalic acid

This reaction illustrates the stability of the pyridine ring since it is the benzene ring that is destroyed by the oxidation. It is of importance in confirming the structure of quinoline, since it indicates the points of union between the benzene and pyridine rings.

8-Hydroxyquinoline is used in a method for the quantitative determination of metals, especially aluminum.

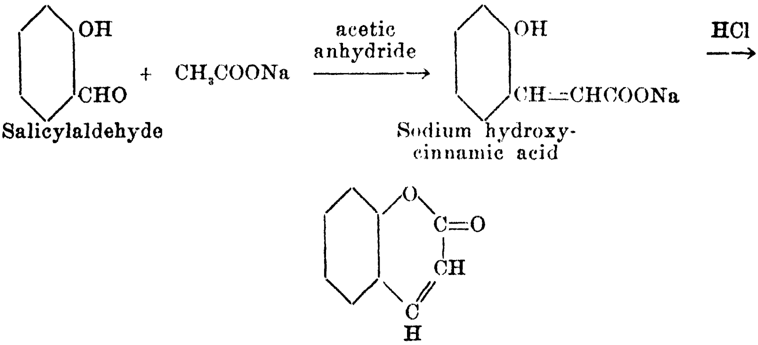
Isoquinoline.—If the fusion of the benzene ring with pyridine takes place in the β-γ-position of the pyridine nucleus, the compound formed is known as isoquinoline. Isoquinoline can be viewed as naphthalene in which a CH group in the β-position has been replaced by a nitrogen atom.



Isoquinoline

Isoquinoline occurs along with quinoline in coal tar. The alkaloids, papaverine and codeine, are derivatives of isoquinoline.

Coumarin.—Coumarin is a sweet-smelling substance with the odor of new-mown hay. It occurs in melilot and the tonka (tonquin) bean. Industrially, it is prepared by heating salicylaldehyde with sodium acetate and acetic anhydride (Perkin synthesis).



Salicylaldehyde

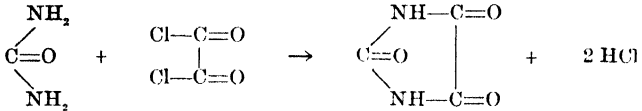
Sodium hydroxy-cinnamic acid

Coumarin

Coumarin often is one of the ingredients of artificial or imitation vanilla flavorings. This compound has not proved to be entirely satisfactory for this purpose, since it tends to give a harsh flavor to the mixture. It is used also for flavoring tobacco, and in perfumery.

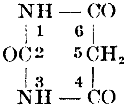
Other Heterocyclic Compounds

Ureides.—The reaction of urea with dicarboxylic acids leads to the formation of compounds known as ureides. The ureide of oxalic acid is formed by the reaction of urea and oxalyl chloride.



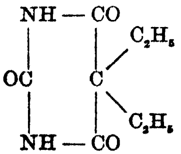
Urea Oxalyl chloride Parabanic acid (Oxalyl urea)

Of greater technical importance is the ureide of malonic acid, barbituric acid.

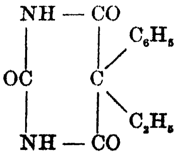


Barbituric acid
(Malonyl urea)

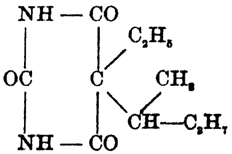
Barbituric acid is the parent substance for a number of important drugs used as hypnotics. In 1903 Fischer showed that diethylbarbituric acid, veronal, or barbital, was an excellent hypnotic. Since that time, this and related compounds have become of great importance to the chemical and the medical world. Compounds in which the number 5 carbon atom of barbituric acid is substituted by alkyl groups of varying complexity are used as hypnotics, anesthetics, anticonvulsants (as in epilepsy, eclampsia), and preanesthetic sedatives. Given prior to inhalation anesthesia, they make anesthesia easier and lessen the amount of general anesthetic required. A few of these compounds are:



Barbital
(Veronal)
(Diethylbarbituric acid)



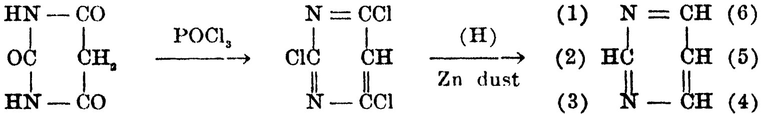
Phenobarbital
(Luminal)
(Phenylethylbarbituric acid)



Pentobarbital
(Nembutal)
(Ethyl, 2-secondary amylbarbituric acid)

These compounds are only slightly soluble in water; therefore, their alkaline salts (Na, Mg, Ca, which are very water soluble, are employed in medicine. These drugs can be injected or given by mouth. Their effect depends on the structure of the particular drug, the means of administration, and the dose. In small doses the barbiturates, in general, act as sedatives; in intermediate size doses, as hypnotics; and in large doses, as anesthetics. However, digestive and other disturbances sometimes follow their use, and research is being carried on to find substitutes that do not have these disadvantages. Some thiobarbiturate compounds, in which thiourea replaces urea, recently have been shown to be successful as hypnotics. An example is pentothal, the sulfur analogue of pentobarbital.

Pyrimidines.—The cyclic structure present in barbituric acid and its derivatives is known as the pyrimidine nucleus. The simplest compound containing this nucleus is pyrimidine, obtained by treating barbituric acid with phosphorus oxychloride, followed by the reduction of the resulting trichloroderivative.



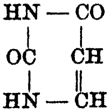
Barbituric acid

2,4,6-Trichloropyrimidine

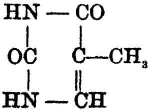
Pyrimidine

For convenience in naming the derivatives of pyrimidine, the nucleus is numbered, as is shown in the foregoing formula.

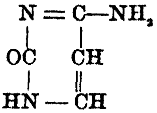
Pyrimidine is a crystalline compound that dissolves readily in water to give neutral solutions. Derivatives of pyrimidine are of physiological importance, since they occur in nucleic acid in cell nuclei. The pyrimidines that have been obtained from nucleic acid are:



Uracil
(2,6-dioxypyrimidine)



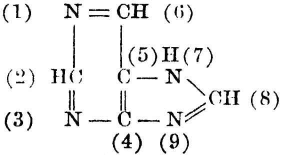
Thymine
(2,6-dioxy-5-methylpyrimidine)



Cytosine
(2-oxy-6-aminopyrimidine)

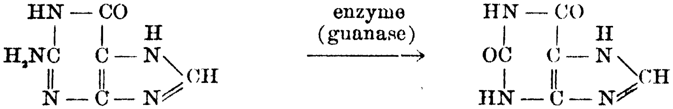
The antineuritic vitamin B_1, thiamin, contains a pyrimidine nucleus in its structure.

Purines.—The purines occur in nucleic acids. They often are designated as diureides, since they contain two urea residues. The parent substance of this class of compounds is purine. It does not occur in nature, but it has been synthesized and shown to possess the following structural formula:



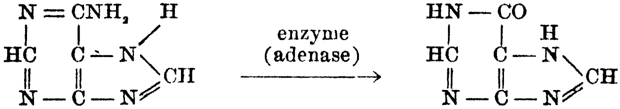
Purine

Guanine and adenine are the two purines that occur naturally in nucleic acids. Xanthine and hypoxanthine are derived from these by the action of enzymes or acids.



Guanine
(2-amino-6-oxypurine)

Xanthine
(2,6-dioxypurine)



Adenine
(6-aminopurine)

Hypoxanthine
(6-oxypurine)

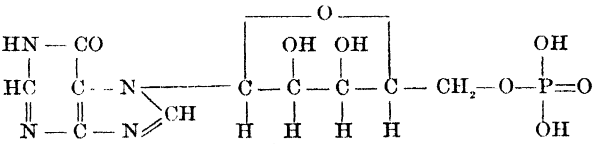
Guanine occurs in significant amounts in fish scales and in the skin of reptiles and amphibia. The crystalline compound accounts for the shiny appearance and iridescent coloring of the body coverings.

Adenine is perhaps the most widely distributed purine base. It is one of the compounds that participates in the chain of reactions that occurs during muscle contraction. This process is discussed more fully in the chapter on carbohydrate metabolism (see page 611).

Nucleic acids. Nucleic acids have been obtained from the nuclear material of numerous plant and animal tissues. Combined with a basic protein, the nucleic acids are the building material of chromatin in all cell nuclei. Chromosomes, which transmit all hereditary characteristics, are derived from chromatin. Hence, the nucleic acids are a part of the material that determines such physical characteristics as height, color of the hair, etc., as well as mental traits and aptitudes.

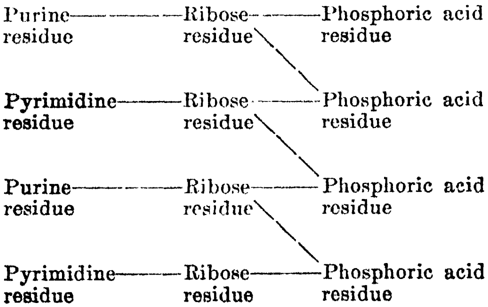
The structure of the nucleic acids is fairly well known. Careful hydrolysis of a nucleic acid yields *nucleotides,* each consisting of residues of a purine or pyrimidine base, sugar, and phosphoric acid. Nucleic acids usually are said to contain four nucleotides, but a few containing a greater number have been isolated. A typical nucleic acid is represented diagrammatically at the bottom of this page.

Particular nucleotides that have been isolated and their structure determined are inosinic acid, guanylic acid, and adenylic acid. Crystalline inosinic acid was isolated from beef extract in 1847 by Leibig. It is composed of hypoxanthine, D-ribose, and phosphoric acid combined in the following manner:



Inosinic Acid

The nucleotides, guanylic acid and adenylic acid, are similar in structure to inosinic acid except that guanine and adenine, respectively, are the purine bases involved in the structure.



Structure of a Typical Nucleic Acid

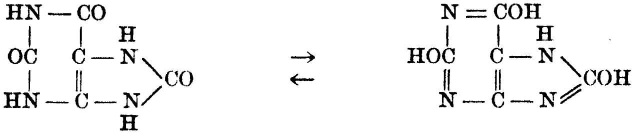
Nucleotides can be further hydrolyzed to give compounds called *nucleosides,* which are the combination of a purine or pyrimidine base with ribose or desoxyribose. The compositions of some of the known nucleosides are:

Inosine contains hypoxanthine and a pentose
Guanosine contains guanine and a pentose
Adenosine contain adenine and a pentose
Uridine contains uracil and a pentose
Cytidine contains cytosine and a pentose
Thymidine contains thymine and a pentose

Uric acid. Uric acid is the end product of purine metabolism in man and the higher apes. The normal person excretes about 0.5 to one gram of it per day in the urine. In certain abnormal conditions, such as gout, imperfect elimination of uric acid results in a deposition of insoluble salts of uric acid in the joints.

In birds and reptiles the chief end product of all protein metabolism is uric acid, which is eliminated in the excreta. Approximately 25 per cent of the total weight of the "guano" (excretions of birds) of the South Sea Islands is ammonium urate; uric acid sometimes is isolated from this source.

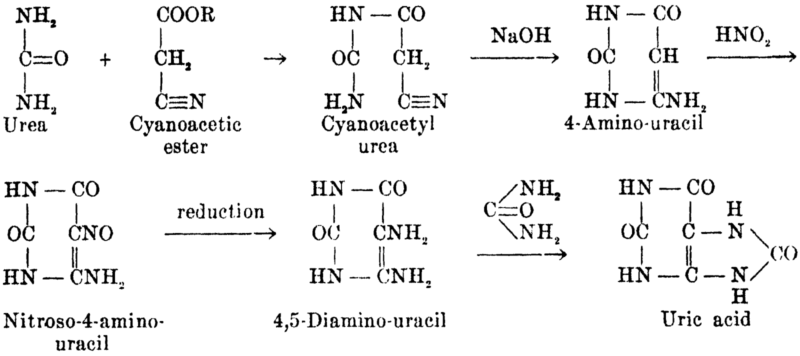
Uric acid, as well as the other purine and pyrimidine compounds, is capable of keto-enol isomerism. The enol form is able to form salts, which explains the solubility of uric acid in dilute alkalies.



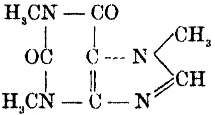
Keto form of uric acid

Enol form of uric acid

A method of synthesizing uric acid that can be used also for the synthesis of other purines was introduced by Traube. In this method, urea is condensed with cyanoacetic ester to form cyanoacetyl urea. This compound is transformed by treatment with alkali into 4-amino-uracil. By the action of nitrous acid, a nitroso-amino-uracil is formed, which is easily reduced to 4,5-diamino-uracil. Upon fusion of 4,5-diamino-uracil with urea, uric acid is obtained in good yield.



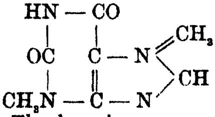
Methyl purines. The three methyl purines that we shall discuss are not found as constituents of nucleic acids. They satisfy the definition of an alkaloid and so could be considered with the alkaloids, but it seems more logical to consider them with the other purine derivatives. Caffeine (1,3,7-trimethyl-2,6-oxypurine), one of the most common methylpurines, occurs to the extent of about 1.5 per cent in coffee. Tea may contain as much as 5 per cent.



Caffeine
(theine)

Caffeine is a white powder that is very soluble in hot water. It is a stimulant to the central nervous system, and a diuretic. The annual U. S. production of caffeine amounts to about 1,000,000 pounds. The foremost use is in the preparation of cola drinks.

Theobromine (3,7-dimethyl-2,6-dioxypurine) is present to the extent of about 2 per cent in cocoa and chocolate. Theobromine has a stimulating effect on the body but not so great as caffeine; it is more effective as a diuretic.



Theobromine

Theophylline (1,3-dimethyl-2,6-dioxypurine) is isomeric with theobromine. It is employed in medicine as a diuretic.

Study Questions

1. Why are anhydrides and lactones usually not considered with the heterocyclic compounds?
2. What is the name of the five-membered ring that contains four carbon atoms and an oxygen atom?
3. What heterocyclic compound containing sulfur in the ring is a common contaminant of benzene? How can it be removed?
4. Describe a chemical test for detecting the presence of pyrrole in an unknown solution.
5. By means of an equation, show the progressive reduction of pyrrole.
6. What are some important chemical compounds that contain pyrrole rings in their structure?
7. What is the name of the heterocyclic compound having the same formula as benzene except that a nitrogen atom replaces a CH group?
8. Write the formula for nicotinic acid. What is the chemical name for this compound? What is its importance?
9. What is the name of the completely saturated (hydrogenated) derivative of pyridine? For what is this compound used?
10. Write formulas for two heterocyclic compounds that are formed in the intestinal tract as the result of bacterial putrefaction of protein material.
11. For what is heteroauxin used?
12. What type of compounds can be prepared by the Skraup synthesis?
13. How does isoquinoline differ from quinoline in structure?
14. Write the formula for coumarin. For what is this compound used?
15. What is the name of the ureide of malonic acid? What are some important derivatives of this compound and for what are they used?
16. Show how the pyrimidine nucleus is numbered to facilitate naming derivatives of this compound. Show numbering of the atoms in the purine nucleus.
17. Name four pyrimidine derivatives found in nucleic acid.
18. Which of the vitamin B factors contain a pyrimidine nucleus in their structures?
19. What two purine bases are known to occur in nucleic acids?
20. Of what physiological importance are nucleic acids?
21. Show diagrammatically how nucleotides and nucleosides are related to nucleic acids.
22. Write formulas for the two tautomeric forms of uric acid.
23. What physiological effects do caffeine and theobromine exert on the body?
24. Name at least four heterocyclic compounds that are components of coal tar.

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CHAPTER XX

ALKALOIDS

Introduction.—A satisfactory definition for alkaloids is difficult to formulate, but one that is satisfactory for most purposes is the following: *Alkaloids are basic substances of plant origin that contain at least one nitrogen atom in a heterocyclic ring.* They usually, although not always, possess marked physiological activity. Alkaloids do not occur in all plants. Very few of the monocotyledons, excepting the lilies, contain alkaloids. Most of the dicotyledons contain alkaloids. Some of the plant families that contain appreciable quantities of alkaloids are:

Leguminosae—the legumes, lupines.
Papaveraceae—poppies, opium poppy.
Solanaceae—nightshade, belladonna.

Different species of plants vary as to the part of the plant that has the highest alkaloid content. For example:

Leaves are used as the source of cocaine.
Seeds are used as the source of strychnine.
Bark is used as the source of quinine.
Roots are used as the source of berberine.
Sap is used as the source of morphine.
Fruit is used as the source of piperine.

Alkaloids rarely occur free in the plants, but they are present as the salts of such organic acids as malic, tartaric, citric, oxalic, tannic, and succinic. In the case of some alkaloids, they are associated with a special acid; e.g., morphine is associated with "meconic" acid, and quinine, with "quinic" acid.

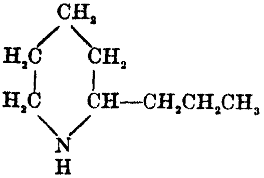
Isolation of the Alkaloids.—Alkaloids can be separated from the plant by grinding and mixing the ground-up material with lime or magnesia. The alkaloids thus liberated can then be obtained by extraction with organic solvents, such as chloroform, ether, and benzene; or by steam distillation. A second method of obtaining alkaloids is by extracting the finely ground material with mineral acid, such as hydrochloric acid. The mineral acids form soluble salts with the alkaloids, and the alkaloids are precipitated from the acid solution by the addition of a weak base, such as ammonium hydroxide or sodium carbonate. The alkaloids separated by either method of isolation can be purified by crystallization of their salts. Reagents such as picric acid, phosphotungstic acid, tannic acid, and potassium mercuric iodide are known as *alkaloidal reagents,* because they are used for the isolation, identification, and estimation of alkaloids. Repeated crystallization of the alkaloidal salts of these reagents gives pure substances. The free alkaloid can be obtained after removing the precipitating agent by treatment with weak alkali.

Physical Properties of Alkaloids.—The majority of alkaloids are white crystalline solids, but berberine is yellow. Nicotine and coniine are liquids. As a rule, alkaloids have a bitter taste, but piperine, obtained from pepper, is tasteless. The pungent taste of pepper is due to an essential oil. The majority of alkaloids are insoluble in water, but nicotine is an exception, being soluble in water. Most alkaloids are optically active, the majority being levororotatory.

Classification of Alkaloids.—Alkaloids can be classified on the basis of their source or on the basis of the heterocyclic nucleus that they contain. We shall use the latter system.

Pyridine Group.—*Coniine,* the alkaloid with the simplest chemical structure, belongs to the group of pyridine alkaloids. It has an interesting historical background. The Greek philosopher, Socrates, was put to death by being forced to drink an extract of deadly hemlock. The coniine present in the extract was responsible for his death.

Coniine was the first alkaloid to be synthesized. The synthesis was carried out by Ladenburg in 1886.

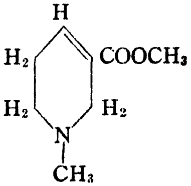


Coniine

Coniine is an oily, colorless, strongly alkaline liquid that is slightly soluble in water. It is a deadly poison when taken in more than extremely small quantities, causing paralysis of the motor nerve endings and depression of the central nervous system.

Piperine, $C_{17}H_{19}O_3N$, is the alkaloid of pepper. It occurs in the black and white peppers of commerce to the extent of 5 to 9 per cent. It has no marked physiological action.

Arecoline is the principal alkaloid of the fruit of the betel nut palm, *Areca catechu*. The seeds of the fruit are used as a mild stimulant by some 200,000,000 persons in India, the Philippines, and the islands of the Pacific and Indian Oceans. Betel chewing is more widespread than is the use of tobacco. The chew consists of a piece of areca nut mixed with some lime and a little gambier, tobacco, or catechu, and rolled in the leaf of the betel pepper. This combination is chewed throughout the day, and often is held in the mouth during the night. It stimulates a copious flow of saliva that is colored blood red by the action of the lime and gambier on the coloring matter of the areca nuts. The teeth are quickly blackened. The craving for the drug is intense, but the habit does not appear to cause any degeneration. Several alkaloids are present in the areca nuts, but the physiological action appears to be due mainly to arecoline, present to the extent of about 0.1 per cent. The alkaloid also is employed as a vermifuge in veterinary medicine.



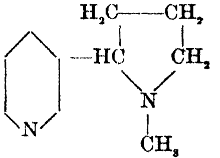
Arecoline

Pyridine-Pyrrolidine Group.—*Nicotine*, the principal alkaloid of tobacco, is a representative of the pyridine-pyrrolidine group of alkaloids. The nicotine content of tobacco varies from 1 to 10 per cent, although the average is usually about 4 per cent and rarely exceeds 6 per cent. Nicotine is combined in the plant with malic and citric acids. It can be conveniently isolated by extracting raw tobacco with water, liberating the alkaloid with alkali, and distilling with steam. Pure nicotine is a colorless, oily, strongly basic, levorotatory liquid. It is readily soluble in alcohol and ether, and is miscible with water below 60° C.

Nicotine in small quantities has the property of causing an initial and transient stimulation. In larger amounts the alkaloid causes dizziness, perspiration, an abnormally large secretion of saliva, and intestinal disturbances. The fatal dose for man is about 60 milligrams.

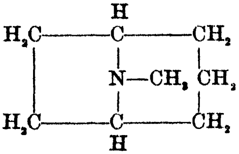
Large quantities of nicotine are used as an insecticide. It is incorporated with soap and oil to form emulsions used in plant sprays. "Black Leaf 40" contains nicotine sulfate. It also can be absorbed on inert substances to give the so-called "nicotine dusts" employed in orchards and gardens for controlling insect pests. Powders containing nicotine are used for the eradication of mites and lice on poultry. The annual world production of tobacco for human consumption and insecticidal use amounts to more than 2,000,000 tons. This amount of tobacco contains about 60,000 to 70,000 tons of nicotine.

Nicotine was synthesized by Pictet in 1904.



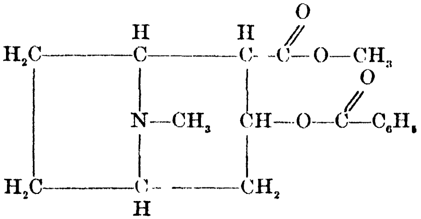
Nicotine

Tropane Group.—Most of the alkaloids occurring in the Solanaceae belong to the tropane group. These alkaloids can be regarded as derivatives of the heterocyclic compound, tropane.



Tropane

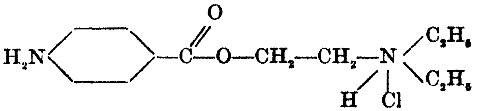
A prominent member of this group is *cocaine.* It is obtained from the leaves of the coca plant, a South American shrub that bears leaves similar to those of the tea plant. Cocaine is a crystalline solid that is slightly soluble in cold water, but readily soluble in alcohol, ether, and benzene. The aqueous solution is levorotatory, is alkaline to litmus, and has a bitter taste. When applied to the tongue, it produces a characteristic numbness. L-Cocaine formerly was highly prized as a local anesthetic because of the short time during which its effect was operative. It was used commonly in dentistry and eye surgery. Cocaine, which was synthesized by Willstätter, has the structural formula:



Cocaine

A disadvantage to the use of cocaine as a drug is that it is somewhat toxic. Taken in small amounts, it has a stimulating effect, but continued use of the alkaloid is habit forming and leads to mental deterioration and insanity. Many daring crimes are committed while criminals are under the influence of cocaine. Solutions of cocaine prepared for hypodermic use are unstable and spoil readily.

In order to overcome these disadvantages inherent in cocaine, substitutes, which are *not* alkaloids according to our definition, have been synthesized for the purpose of preserving its local anesthetic action and eliminating its undesirable properties. It was found that the methyl ester group was responsible for the habit-forming properties, while the local

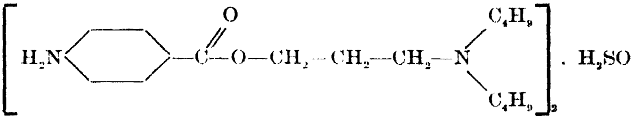


Procaine hydrochloride

anesthetic properties mainly were associated with the benzoyl- and nitrogen-containing part of the molecule. One of the compounds resulting from these researches was procaine ("Novocain").

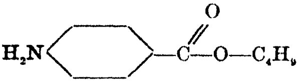
Instead of free procaine, the hydrochloride form is used for hypodermic injections because it is water-soluble. The primary amino group with its basic properties is introduced on the benzene ring in order that the hydrochloride will be essentially neutral. Procaine is only one-seventh as toxic as cocaine, and gives stable solutions. It cannot be used as a surface anesthetic. Adrenaline, which constricts the capillaries, often is used with procaine in dentistry and surgery to prevent rapid spreading of the local anesthetic. The presence of adrenaline also reduces bleeding.

A cocaine substitute that does have surface anesthetic properties is butyn.



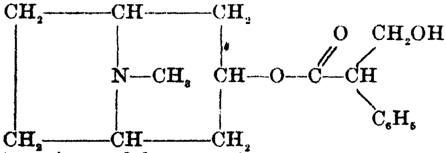
Butyn

Closely related to butyn is butesin, another compound which also has surface anesthetic properties. The use of butesin picrate as a treatment for burns has been mentioned earlier (page 435).



Butesin

Atropine was isolated as early as 1831 from the roots of the deadly nightshade, *Atropa belladonna*. The formula of atropine that is accepted today was proposed by Willstätter.

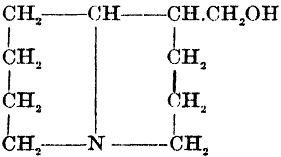


Atropine and hyoscyamine

Atropine is a racemic mixture, and rarely occurs as such in plants. Usually, it is obtained from its naturally occurring levorotatory isomer, hyoscyamine, by racemization of the latter with alkali. Because of this relationship, the foregoing formula can be used to represent the structural formula of both atropine and hyoscyamine.

Atropine is used as a mydriatic (causes dilation of the pupil of the eye). This effect is due to the paralysis of the motor nerve endings in the circular muscle of the iris. Atropine is used also as an antidote for toadstool poisoning, since it paralyzes all the nerve endings that this poison (muscarine) stimulates. Even in small doses atropine reduces glandular secretion, diminishes the flow of saliva, perspiration, and mucus; it is employed in medicine for these purposes. Jimson weed, containing the alkaloid, hyoscyamine, or a structurally related alkaloid, hyoscine, occasionally causes stock poisoning (see page 541).

The lupines are important stock-poisoning plants on the ranges of the Western states and the Pacific coast. There are about 150 species in the genus *Lupinus*. Some of these species are very poisonous due to their alkaloidal content; others cause poisoning only under particular circumstances; and some are harmless under range conditions. Since the lupines are legumes, those species that do not contain alkaloids are potentially valuable forage plants. A number of alkaloids have been isolated from the various species of lupine. *Lupinine* is one that is widely distributed. The following formula was proposed by Karrer.

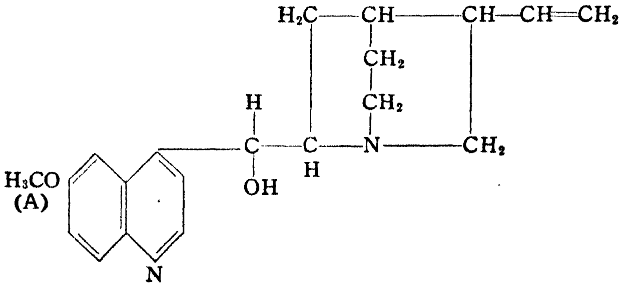


Lupinine

The correctness of this formula was demonstrated by its synthesis (Clemo). The lupine alkaloids act upon the central nervous system to disturb the motor functions. Different symptoms are manifested by animals poisoned by different species of lupine. Sheep poisoned on some species of lupine exhibit symptoms indicative of nerve stimulation, whereas poisoning by other species induces symptoms of depression only. The motor functions in cattle and horses are depressed in lupine poisoning.

Quinoline Group.—The principal members of the quinoline group are the cinchona alkaloids, of which *quinine* and *cinchonine* are of most practical importance. Cinchona alkaloids occur in the various species of the two Rubiaceae genera, *Cinchona* and *Remijia,* which are native to the eastern slopes of the Andes. Species of cinchona grow most abundantly at altitudes of 5,000 to 8,000 feet, and rarely are found below 2,500 feet elevation. The South American Indians probably used cinchona bark for the treatment of fevers long before the coming of the Spaniards. It was introduced in Europe about 1632, and was definitely in use by 1638. The demand for cinchona bark became so great that the total extinction of the trees in South America was threatened. The danger directed attention to the possibility of cultivating the trees in India, Australia, and Java. Mainly as a result of the close supervision and aid given by the Dutch East India Government, Java has become the most important cinchona-producing district in the world. The annual production of quinine sulfate before World War II averaged between 600,000 and 700,000 kilograms, 90 per cent of which came from the Dutch East Indies.

Quinine and cinchonine both were isolated from cinchona bark in 1820 by Pelletier and Caventou. The formula of quinine was established by the synthesis of the alkaloid by two young scientists, Woodward and Doering, in 1944.



Quinine

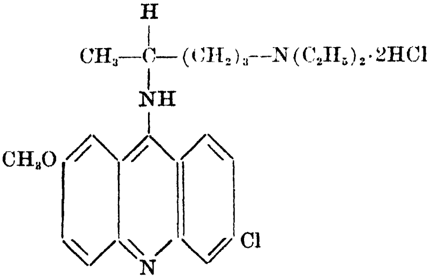
The structure of cinchonine differs from that for quinine only in that there is a hydrogen at (A) instead of a methoxy group.

Quinine is used to reduce fever and in the treatment of malaria. The physiological action of cinchonine is somewhat similar to that of quinine, but less pronounced. Certain tonics contain quinine, strychnine, and some inorganic salt of iron.

The search for antimalarials became of prime importance to the United States after the Japanese attack on Pearl Harbor. The United States was faced with the necessity of fighting a major war in some of the world's worst malaria-infested countries. The problem was intensified after the loss of the East Indies to the Japanese. This region previously had supplied 90 per cent of world's production of quinine, hitherto the standard antimalarial drug. In the late fall of 1943 the search for antimalarials was intensified under the auspices of the Office of Scientific Research and Development. The program grew into what was probably the most intense mass attack made on any chemotherapeutic problem. According to Elderfield, during the period 1941-1946 approximately 14,000 compounds were tested for their antimalarial effect. Among these about 70 classes of organic compounds showed some antimalarial action. Further investigation has narrowed the field to four or five groupings.

The human malaries that are most widespread are *Plasmodium vivax* and *Plasmodium falciparum.* The first type is prone to recur periodically even though the clinical symptoms have been alleviated by the administration of suitable drugs. In contrast, if the attack of *Plasmodium falciparum* has been adequately treated, there is little likelihood of recurrence of the manifestations of the disease. This type, known as malignant tertiary malaria, frequently results in fatalities unless a suitable drug is administered promptly after the first attack. It is to be emphasized that the so-called antimalarial drugs commonly used at the present time, with the possible exception of plasmochin and some of its chemically related compounds, act only as suppressive agents. This means that in the case of *P. vivax* the individual may be infected, but may show no symptoms of the disease as long as he adheres to a prescribed dosage of the suppressive drug. As soon as the treatment is discontinued, typical attacks may occur.

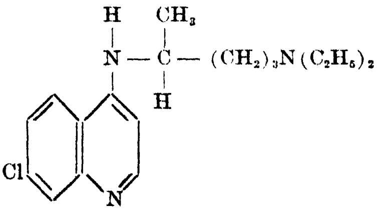
"Atabrine" (mepacrine, quinacrine) probably is the most widely used of the suppressive type of drugs for malaria.



"Atabrine" hydrochloride

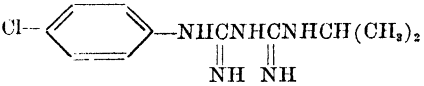
The advantages of this drug over quinine are that the margin of safety between the therapeutic and the toxic dose is relatively large, it can be safely administered in pregnancy when quinine is contraindicated, and it does not have as intensely bitter a taste as quinine.

The antimalarial, chloroquine ("Aralen," SN-7618), was one of the results of the O.S.R.D. program. It is said to be twice as effective against the common human malarias as is "Atabrine." In addition, it is capable of terminating a clinical attack of *P. falciparum* by oral administration whereas "Atabrine" must be injected intramuscularly. Furthermore, chloroquine does not cause the unsightly yellow pigmentation resulting from "Atabrine" administration. One tablet a week of chloroquine is an effective suppressive while "Atabrine" and quinine require daily doses.



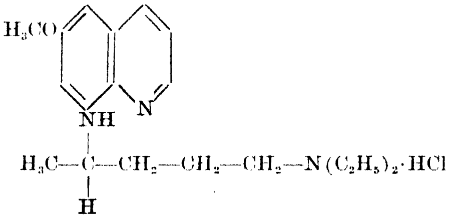
Chloroquine

Another effective suppressive for malaria developed in England during World War II is chlorguanide ("Paludrine"). Clinical trials have shown that small doses at infrequent intervals are sufficient to prevent the attacks of *P. vivax.*



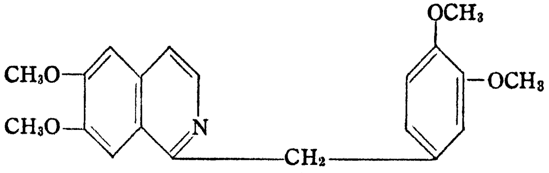
Chlorguanide

"Plasmochin" (pamaquin) is the best known of the curative drugs for *P. falciparum.* It has been shown to effect a fair percentage of cures of relapsing form of malaria when administered in conjunction with quinine or "Atabrine."



"Plasmochin" hydrochloride

Isoquinoline Group.—The alkaloids of this group are obtained chiefly from the botanical family *Papaveraceae.* Papaverine is one of the alkaloids present in opium, the sun-dried latex of the unripe fruit of the opium poppy. The synthesis of papaverine by Pictet and Gams proved it to have the following structure:



Papaverine

Morphine **is the alkaloid that is chiefly responsible for the physiological action of opium. Opium may contain from 3 to 23 per cent of morphine. It was the first alkaloid to be**

isolated from a plant source. Sertürner, a German apothecary, in 1806 described its basic properties and called it ''morpheum.''

Morphine has a depressing action on the central nervous system. In very small amounts (16 mg. or less) it relieves pain. When taken in larger doses, the drug produces sleep. Continued use leads to greatly increased tolerance and the dangerous probability of becoming addicted to the drug. A characteristic property of morphine, and, indeed, of alkaloids in general, is a reduction of peristaltic action. Due to this property, morphine occasionally is used in the treatment of diarrhea. In other cases where drugs containing alkaloids are administered, it is necessary sometimes to add a laxative to counteract the effect of the alkaloid.

About 25 alkaloids occur in opium. This is the greatest number of alkaloids that have been isolated from any single plant source.

Berberine, $C_{20}H_{19}O_5N$, probably is more widely distributed than any other alkaloid. It has been found in the plants of six botanical families and in twelve different genera. Berberine, which is a *yellow* crystalline solid, can be isolated conveniently from barberry root bark. The alkaloid is soluble in water to the extent of one part to four and a half parts of water. Such an aqueous solution is extremely bitter. Berberine sometimes is used in tonics.

Strychnos Alkaloids.—*Strychnine* and *brucine,* the most important members of the Strychnos class of alkaloids, occur in nux-vomica seeds and in Ignatius beans. Much labor and ingenuity have been expended on the difficult problem of determining the constitution of these two alkaloids, but as yet the efforts have not been very successful. Strychnine, $C_{21}H_{22}O_2N_2$, is highly toxic. In poisonous doses it causes convulsions involving most of the muscles of the body. It often is employed as a poison for small animals.

Strychnine, in very small doses, has a stimulating effect and is used in certain tonics. It has been reported that some Alpine mountain climbers use strychnine to give them greater endurance.

Brucine, $C_{23}H_{26}O_4N_2$, is a dimethoxy derivative of strychnine. It is less toxic than strychnine, but its lethal dose is so close to the therapeutic dose that it is not employed in medicine. It is a rather common component of rat poisons. Brucine and strychnine are used in the resolution of racemic mixtures of optically active acidic substances.

Curare is the name applied to plant extracts formerly used as arrow-tip poisons by Indians in tropical South America. The colorful history and the properties of curare are vividly described by McIntyre in his recent book. Early explorers in the sixteenth and seventeenth centuries had a number of unfortunate encounters with this deadly arrow poison. When injected intramuscularly it is capable of producing muscle paralysis in a short time, and death occurs from respiratory or cardiac failure. When taken by mouth, curare is said to be nontoxic, probably due to its slow absorption by the intestinal mucosa, and also to its rapid elimination from the body. A few of the early explorers were able to make friends with the Indians, and to find out how curare poisons were prepared. In general, the basic process was very simple, with a goodly quantity of magic and witchcraft sprinkled in by the natives. The bark from a number of suitable trees was crushed and a water infusion made. This was evaporated down and a gelatinous substance added so that the poison would be thick enough to adhere to the arrow tips. Of a fairly large number of plants that could be used for the preparation, *Strychnos toxifera* yielded the most powerful curare poison.

Although the Indians no longer prepare curare as an arrow poison, these alkaloids are finding considerable use in the medical field because of their therapeutic properties. It has been used with varying degrees of success in the treatment of tetanus, poliomyelitis, hydrophobia, and epilepsy. Some workers say that it can be used to advantage with all volatile anesthetics because muscle relaxation can be obtained with less anesthesia than would otherwise be possible.

There are some 30 quaternary alkaloids named *curarines* that have been isolated from crude curare. Of these, D-tubocurarine,

$C_{38}H_{44}O_6N_2$, is the only one that is available now in this country for medicinal purposes.

Colchicine, $C_{22}H_{25}O_6N$, is obtained from the seeds and corms of the autumn crocus, *Colchicum autumnale.* The colchicine of commerce usually is encountered in the form of yellow flakes or powder. According to our definition of alkaloids, colchicine is not a true alkaloid, since it does not contain nitrogen in a heterocyclic ring. The exact structural formula of colchicine is still somewhat uncertain.

Colchicine is used in medicine for the relief of the pain of rheumatic fever and gout. Its interest to the biologist lies in the discovery by Blakeslee that, when plants are treated with colchicine, there is a doubling of their chromosome number. Tetraploids thus can be produced from diploids. The significance of this observation to the horticulturist is that the doubling in the number of chromosomes also is associated with an approximate doubling of the cell volume. In other words, a possibility is created of developing plants that are twice the size of the present varieties.

Origin of Alkaloids in Plants.—Several theories have been advanced to explain the origin and function of alkaloids in the plants. One theory is that the alkaloids are waste products of protein metabolism, and correspond to urea and uric acid in animals. Another theory, and the one that seems best to fit the facts, is that alkaloids are by-products in the formation of proteins.

Stock-Poisoning Plants.—A short section on stock-poisoning plants will be included in this chapter, since most stock-poisoning substances are alkaloids. The importance of these harmful plants is better appreciated when it is realized that the loss of livestock due to plant poisoning is estimated to exceed $2,000,000 annually.

In addition to the lupines, which already have been mentioned, other plants that owe their poisonous character to their alkaloidal content are members of the larkspur, *Delphinium,* species. Although 26 possibly poisonous species growing in the United States have been listed, very little is known concerning the structure of the alkaloids of these plants. The greatest concentration of alkaloids generally occurs in the seed, which may contain as high as 2 per cent alkaloids.

The cattle poisoning from eating these plants is known as delphinosis. This causes more losses among range cattle in the West than any other plant except locoweed. Cattle and horses are poisoned by the plant, but sheep are not affected. Fairly large quantities, 2 to 3 per cent of the animal's body weight, must be eaten before toxic symptoms appear. The general symptoms of delphinosis are staggering gait, nausea, and, lastly, convulsions; hence the common names for the plants are staggerweed and poison weed.

Another important group of poisonous plants is the death camass, which also owes its toxic properties to the presence of alkaloids. The death camass constitutes a serious menace to the sheep grazing industry. The constitution of the alkaloids in these plants is as yet uncertain.

A great number of plants contain poisons termed *resinoids*. This name is applied because these substances have resinlike characteristics. The resinoids are difficult to purify. Most of them have not been crystallized, and their chemical structures are problematical. The poisonous substance in the very toxic water hemlock *(Cicuta vagans)* is the resinoid *cicutoxin*. Members of the species *Cicutas* are distributed widely in low swampy places. Poisoning from them often occurs in the spring when the ground is soft and the roots can be readily pulled from the soil. Children sometimes are tempted to eat the roots because of their attractive odor, and numerous fatalities have been reported from this cause. The various species of water hemlock are said by Couch to be, without doubt, the most poisonous plant that grows in the United States.

Next to the water hemlock in toxicity is the whorled milkweed. Three ounces of the fresh plant are sufficient to cause the death of an adult sheep. The poisonous substance in this plant also is a resinoid.

Oxalic acid is the poisonous substance in another group of plants. An important member of this group is the species of greasewood, *Sarcobatus vermiculatus,* which grows abundantly in the arid regions of the Western states. In one instance at

Harper, Oregon, 1,000 of a flock of 1,700 sheep that grazed during the day on a greasewood area died during the night.

The plants that probably cause the greatest loss to the stock-raising industry are the species of locoweed. Animals that are poisoned from eating locoweed exhibit the symptoms of "loco disease," the name being derived from the Spanish word for "crazy." White and purple locoweeds are widely distributed over the Great Plain states, and losses of horses, cattle, and sheep from locoism have been large. In Colorado the losses were so serious that the state expended $450,000 during a period of nine years in an attempt to eradicate the weed. Animals affected with locoism manifest muscular incoordination, and there are disturbances of vision. The animal is unable to judge the height of objects on the ground. Thus, in stepping over a rope lying on the ground, the horse may step high enough to clear two feet.

The particular substance responsible for the symptoms of locoism has been isolated and analyzed, but, unfortunately, the chemical structure as yet has not been determined.

Solanine is an alkaloidal glucoside that occurs in potatoes. On hydrolysis, it yields glucose, galactose, rhamnose, and an organic base, *solanidine* ($C_{27}H_{43}ON$). Ordinary potatoes do not contain enough solanine to be toxic, but on long exposure to the sun a green color develops, and such potatoes have a bitter taste. These "sunburned" potatoes may contain 20 to 30 times as much solanine as do normal potatoes. The eating of considerable quantities of them can cause death to man and the lower animals. Solanine also seems to be concentrated in the sprouts of potatoes. A number of deaths of livestock as a result of the consumption of potato sprouts are reported each spring.

The green berries of black nightshade (*Solanum nigrum*) contain solanine and the alkaloid, solanidine. Sheep are most susceptible to this type of poisoning.

Study Questions

1. **Define alkaloids. In what group of plants do alkaloids occur most frequently?**
2. **Describe briefly a process for separating alkaloids from other plant material.**

3. What are some of the characteristic physical properties of all alkaloids?
4. Write the structural formula for the alkaloid with the simplest chemical structure. To what chemical group of alkaloids does it belong? Of what historical interest is this alkaloid?
5. What is the principal alkaloid that acts as a mild stimulant for those who indulge in betel chewing?
6. To what chemical group of alkaloids does nicotine belong? How can the alkaloids be isolated from tobacco? What is the physiological effect of these alkaloids? What are some uses of free nicotine?
7. What are the disadvantages of the use of cocaine as a local anesthetic? Write the structural formula for the compound that now is being used.
8. Name two alkaloids with surface anesthetic properties.
9. What is the relationship of atropine and hyoscyamine?
10. Quinine and cinchonine belong to what chemical group of alkaloids? What is the source of these two alkaloids and for what are they used?
11. What is the chief alkaloid of the opium poppy? What physiological effects does this alkaloid exhibit?
12. What is probably the most widely distributed alkaloid?
13. What is the name of an alkaloidal plant extract that has been used by the Indians in South America as an arrow-tip poison?
14. How does strychnine act as a poison? For what purpose are strychnine and brucine sometimes employed in the chemical laboratory?
15. Of what importance is colchicine?
16. To what substance is the poisonous character of water hemlock due?
17. Why is it not advisable to eat ''sunburned'' potatoes? Why should not potato sprouts be fed to livestock?

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CHAPTER XXI

PROTEINS AND AMINO ACIDS

Introduction.—Proteins are naturally occurring substances of high molecular weight that yield, primarily, amino acids on hydrolysis. The term *protein* comes from the Greek word meaning "holding first place," and this derivation serves to emphasize the importance of proteins from a biological viewpoint. They are one of the three major classes of foodstuff, carbohydrates and fats being the other two. The *chief* function of protein in the diet is to supply material for the building of new cells and cell products, and the replacement of old cells in the body. About 70 to 80 per cent of the living cell is water, and of the remainder, approximately 90 per cent is protein. Proteins, more than any other cell components, serve to give protoplasm its characteristic structure.

The chief elements present in proteins are carbon, hydrogen, oxygen, and nitrogen. In addition, small amounts of sulfur, phosphorus, iron, and iodine sometimes are present. The high content of nitrogen differentiates proteins from the other classes of foodstuff. The analysis of the protein content of a material is based on its nitrogen content. Usually a pure protein is about 16 per cent nitrogen, and the percentage of nitrogen multiplied by 6.25 gives the approximate percentage of protein in a biological material. The factor 6.25 is obtained by dividing 100 by 16. In the case of wheat flour, however, the factor for conversion of percentage nitrogen to percentage protein is 5.7, because the protein of wheat flour has been found to be 17.5 per cent nitrogen. The Kjeldahl method is the most widely used procedure for the determination of nitrogen in organic materials. This method consists essentially of heating the material with concentrated sulfuric acid in the presence of such catalysts as copper, mercury, or selenium compounds. The carbon and hydrogen in the material are oxidized to carbon dioxide and water, respectively, and the nitrogen is converted to ammonium hydrogen sulfate, which remains in the flask. Excess sodium hydroxide is added to the residual ammonium bisulfate and sulfuric acid in the Kjeldahl flask, and the ammonia liberated is distilled into an excess of acid of a known concentration. The excess of unneutralized acid is titrated with a base, and from the results the amount of ammonia formed can be calculated. The percentage of nitrogen determined by this method, multiplied by the appropriate factor, gives the percentage of protein in the material.

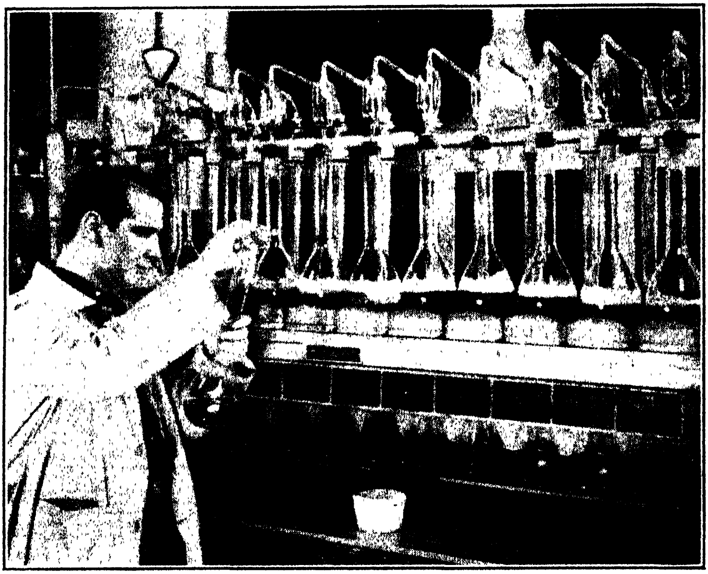


Fig. 63.—Laboratory apparatus for the determination of nitrogen by the Kjeldahl method. The technician is adding sodium hydroxide to a sample preparatory to distillation on the electrically heated units. The glass "traps," shown at the top of the picture, prevent any alkali from being carried over to the receiving flasks during the distillation process. The ammonia and steam, which are volatile, pass through the traps and into a condenser. The condensate is absorbed by standardized acid contained in the Erlenmeyer flasks below the distillation rack. (Courtesy of the Corn Industries Research Foundation.)

Animals cannot synthesize proteins from inorganic forms of nitrogen; hence, the nitrogen for the building of their proteins must be present in the organic compounds in their food. Plants, on the other hand, can utilize nitrates and other forms of inorganic nitrogen in their synthesis of proteins; thus the expression "all flesh is grass." Animals either must get their protein-building material from plants or from other animals that have eaten plants. The proteins that are ingested are hydrolyzed to amino acids in the animal body, and are transported by the blood in this form to the body cells, where they may be resynthesized into proteins. The mysterious property of biological specificity is illustrated by this synthesis, for each organism and each type of cell within the organism apparently possesses its own characteristic protein. Familiar examples of protein materials are egg white, cheese, wool, silk, and hair.

The determination of the exact structure of the different proteins has been attended with many difficulties, and still is largely unsolved. The chemist's first problem in determining the structure of a compound is to obtain a pure product with which to work. Most proteins are gummy substances that form colloidal solutions, and are very difficult to purify. The methods used by organic chemists to purify compounds, such as distillation and sublimation, are not applicable to proteins, since they decompose on exposure to more than moderate temperatures. In one fundamental respect, all proteins are similar—on hydrolysis they yield a mixture of α-amino acids. These substances are the "building blocks" from which the complex proteins are formed. Before proceeding further, therefore, it seems logical to consider the chemistry of the amino acids.

Amino Acids

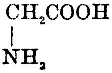
Isolation and Classification.—Amino acids can be obtained from proteins by one of the following methods of hydrolysis:

1. Acid hydrolysis (for example, boiling with 20 per cent hydrochloric acid for twenty-four hours).
2. Alkaline hydrolysis (for example, boiling with 10 per cent sodium hydroxide for ten hours).
3. Enzyme hydrolysis (for example, digesting with trypsin at 37.5° C. and pH 8 for two to three days).

A large number of different proteins are known, but the number of amino acids obtained from them is comparatively small. Only 23 amino acids are known definitely to be present in protein hydrolysates, but the number of ways in which these can be combined to form proteins runs into astronomical figures. The amino acids can be divided into groups according to their structure. In referring to them, their special names are used more often than are their chemical names.

A. *Aliphatic Amino Acids. 1. Monoamino-monocarboxylic acids.*

a. Glycine (aminoacetic acid, glycocoll).

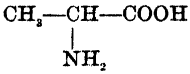


$$\underset{\underset{\displaystyle NH_2}{|}}{CH_2}COOH$$

The simplest amino acid that has been found to be a constituent of proteins is a derivative of acetic acid, and is called glycine. It was discovered in 1820 by Braconnot, who obtained it by treating gelatin with sulfuric acid. Because of its sweet taste he called it gelatin sugar. This amino acid is prepared synthetically by the treatment of monochloroacetic acid with ammonia. The protein containing the highest percentage of glycine is silk fibroin, in which 36.8 per cent of the total nitrogen is glycine nitrogen.

A desirable practice that should have wider adoption is to base amino acid composition on the nitrogen content of the protein. Besides the advantage of uniformity, it makes possible a ready comparison of the results of various investigators. If amino acid composition is based on the weight of protein, comparison of results is not possible unless values for the moisture, ash, and fat contents of the protein are given. All of the amino acid percentages given in this chapter are based on the total nitrogen of the protein.

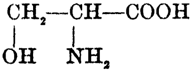
b. Alanine (α-aminopropionic acid).



$$CH_3\text{—}\underset{\underset{\displaystyle NH_2}{|}}{CH}\text{—}COOH$$

This amino acid was isolated in 1875 as a decomposition product of silk. The highest content of alanine, 22.2 per cent, is found in silk fibroin.

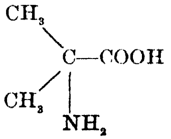
c. Serine (β-hydroxy-α-aminopropionic acid).



$$\underset{OH}{CH_2}—\underset{NH_2}{CH}—COOH$$

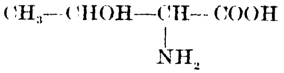
Another amino acid that is a derivative of propionic acid is serine. This acid has an hydroxyl group on the β-carbon. Sericin, a protein obtained from silk, contains 32.9 per cent serine. This is the highest percentage found in any protein.

*d. α-Amino-isobutyric acid.



This amino acid, which was isolated from lupine seed, has no common name. It is the only amino acid known to contain a tertiary carbon atom.

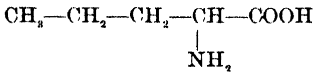
e. Threonine (α-amino-β-hydroxybutyric acid).



$$CH_3—CHOH—\underset{NH_2}{CH}—COOH$$

Threonine was isolated in pure crystalline form in 1935 by Rose and his associates. It must be present in the diet of animals for normal growth to occur. (A complete list of the essential amino acids is given on page 558.)

*f. Norvaline (α-aminovaleric acid).



$$CH_3—CH_2—CH_2—\underset{NH_2}{CH}—COOH$$

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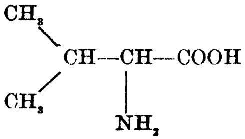
*The amino acids designated by an asterisk in this classification have not met the requirements imposed by Vickery and Schmidt for considering an amino acid a definite product of protein hydrolysis. These criteria are:

1. The amino acid must have been isolated by some worker other than the discoverer.

2. Its constitution must have been established by synthesis and by demonstration of identity between the synthetic product and the racemized natural product, or by actual resolution of the synthetic product and preparation of the optically active natural isomer.

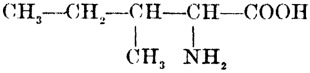
This amino acid was isolated in 1930 by Abderhalden and Bohn.

g. Valine (α-amino-isovaleric acid).



Valine was synthesized in 1906 by Fischer, who coined its name. It is a constituent of the penicillins.

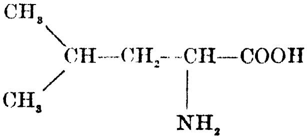
h. Isoleucine (α-amino-β-methylvaleric acid).



$$\mathrm{CH_3—CH_2—\underset{CH_3}{\underset{|}{CH}}—\underset{NH_2}{\underset{|}{CH}}—COOH}$$

This amino acid was isolated in 1903 by F. Ehrlich. It is a widely distributed constituent of proteins.

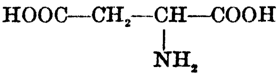
i. Leucine (α-amino-isocaproic acid).



Leucine was isolated from cheese by Proust, who called it "oxide caséeux." He did not recognize it as a decomposition product of proteins. It was identified and named by Braconnot in 1820.

2. *Monoamino-dicarboxylic acids.*

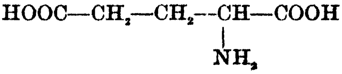
a. Aspartic acid (α-aminosuccinic acid).



$$\mathrm{HOOC—CH_2—\underset{NH_2}{\underset{|}{CH}}—COOH}$$

This amino acid can be obtained from asparagine (the amide of aspartic acid), which is present in *Asparagus officinalis* and many other plants.

b. Glutamic acid (α-aminoglutaric acid).

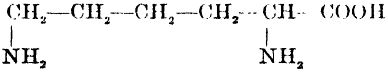


$$\mathrm{HOOC—CH_2—CH_2—\underset{NH_2}{\underset{|}{CH}}—COOH}$$

Glutamic acid is a prominent constituent of gliadin (one of the proteins of wheat); indeed, it comprises about 43 per cent of this protein. The sodium salt of glutamic acid is used widely as a meat flavoring for soups, gravy, etc.

3. Diamino-monocarboxylic acids.

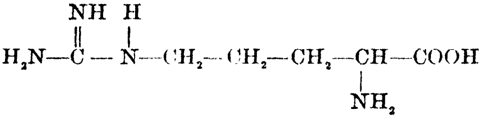
a. Lysine (α-ϵ-diaminocaproic acid).



$$\underset{NH_2}{\underset{|}{CH_2}}—CH_2—CH_2—CH_2—\underset{NH_2}{\underset{|}{CH}}—COOH$$

Drechsel isolated lysine in 1889. The epsilon-amino group of lysine is thought to exist as a free amino group in proteins.

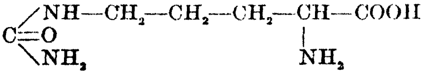
b. Arginine (α-amino-δ-guanidovaleric acid).



$$H_2N—\overset{NH}{\overset{\|}{C}}—\overset{H}{\overset{|}{N}}—CH_2—CH_2—CH_2—\underset{NH_2}{\underset{|}{CH}}—COOH$$

Hedin in 1895 isolated arginine from a protein hydrolysate. It is thought to be present in all vegetable proteins. Some of the simplest proteins, such as salmine from the salmon sperm, contain as much as 88 per cent arginine.

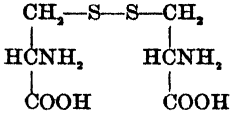
*c. Citrulline (α-amino-δ-carbamidovaleric acid).



Citrulline was first isolated in pure form from the juice of watermelons. It is believed by many to play an intermediate role in the formation of urea in the animal body (see page 649).

4. Sulfur-containing amino acids.

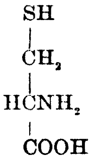
a. Cystine [di(β-thio-α-aminopropionic acid)]



$$\begin{array}{ccc} CH_2 & —S—S— & CH_2 \\ | & & | \\ HCNH_2 & & HCNH_2 \\ | & & | \\ COOH & & COOH \end{array}$$

This amino acid was discovered in 1810 by Wollaston. It is a sulfur-containing amino acid that is a prominent constituent of the protein in hair. The cystine content of human hair is about 16 per cent.

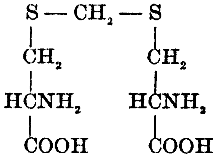
An amino acid that is closely related to cystine is cysteine (α-amino-β-thiolactic acid).



$$\begin{array}{c} SH \\ | \\ CH_2 \\ | \\ HCNH_2 \\ | \\ COOH \end{array}$$

Little doubt exists as to the occurrence of cysteine in native proteins. This amino acid contains the sulfhydryl group (—SH), which is readily oxidized to the disulfide linkage (—S—S—) of cystine. Several methods for the colorimetric determination of cystine depend on its reduction to cysteine, which reacts with some of the reagents to form a colored compound.

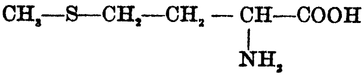
*b. Djenkolic acid.



$$\begin{array}{ccc} S & -\,CH_2\,- & S \\ | & & | \\ CH_2 & & CH_2 \\ | & & | \\ HCNH_2 & & HCNH_2 \\ | & & | \\ COOH & & COOH \end{array}$$

The Dutch workers, van Veen and Hyman, isolated djenkolic acid in 1933 from djenkol nuts. The acid contains two sulfur atoms and two amino groups. In 1936 it was synthesized by du Vigneaud.

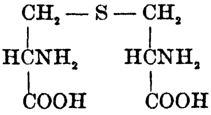
c. Methionine (γ-methylthiol-α-amino-butyric acid).



$$CH_3-S-CH_2-CH_2-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH$$

In 1922 Mueller isolated methionine from casein. This sulfur-containing amino acid is a dietary essential. In the animal body cystine and cysteine can be produced from methionine, but the reverse reaction is not possible. A minimal supply of methionine, which cannot be replaced by cystine or other sulfur-containing amino acids, must be present for an adequate diet. Synthetic methionine is now a commercial product. Its price has fallen from $506 per kilogram in 1945 to $25 per kilogram in 1948.

*d. Lanthionine.

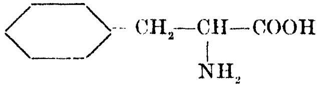


$$\begin{array}{ccc} CH_2 & - S - & CH_2 \\ | & & | \\ HCNH_2 & & HCNH_2 \\ | & & | \\ COOH & & COOH \end{array}$$

This amino acid first was isolated by Horn, Jones, and Ringel in 1941 from wool that had been treated with sodium carbonate. Later it was isolated from other proteins that had been treated with sodium carbonate. It remains to be demonstrated that this amino acid occurs in native proteins.

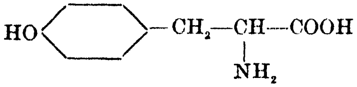
B. Aromatic Amino Acids.

a. Phenylalanine (β-phenyl-α-aminopropionic acid).



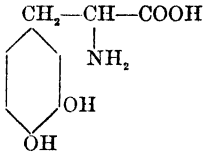
Schulze isolated phenylalanine in 1879. It is the aromatic analogue of alanine.

b. Tyrosine (β-parahydroxyphenyl-α-aminopropionic acid).



Tyrosine was isolated in 1846 by Liebig. It can be considered as the hydroxyl derivative of phenylalanine. Tyrosine, in the presence of tyrosinase and gaseous oxygen, readily forms colored products. The oxidation of tyrosine is responsible for the darkening of apples and potatoes when they are exposed to the air. Tyrosine is unusual among the amino acids in that it is sparingly soluble in water.

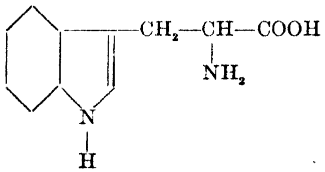
*c. Dopa (3,4-dihydroxyphenylalanine).



This amino acid has never been isolated from a protein, but it occurs free in certain plants. In the presence of dopa oxidase, it is thought to be converted to melanin, the characteristic pigment of skin and hair (see page 654).

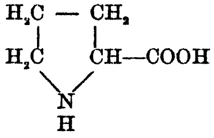
C. Heterocyclic Amino Acids.

a. Tryptophan (β-indol-α-aminopropionic acid).



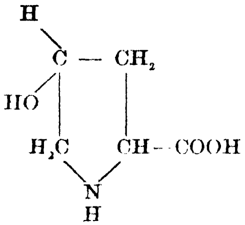
Tryptophan has been detected in seedlings of peas, vetch, and soybeans. Hopkins and Cole isolated it in 1901. Due to the presence of the indol group in tryptophan, it reacts with many reagents to give colored products, which can be used for its identification. Gramicidin, an antibiotic, contains about 40 per cent tryptophan. This is 5 times the quantity present in the protein of highest known tryptophan content.

b. Proline (pyrrolidine-α-carboxylic acid).



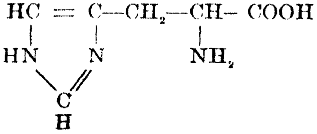
Proline is soluble in alcohol but not in water. It is not a true α-amino acid, but, in reality, is an imino compound (—NH— is called the imino group). The prolamines, a class of proteins obtained from cereal grains, contain a high percentage of proline. Gliadin, from wheat, contains 12 per cent proline. Gelatin contains 15 per cent of this amino acid.

c. Hydroxyproline (4-hydroxy-pyrrolidine-2-carboxylic acid, γ-hydroxyproline).



Hydroxyproline is soluble in water. It differs from proline in the replacement of one hydrogen atom by an hydroxyl group. Fischer isolated it in 1902.

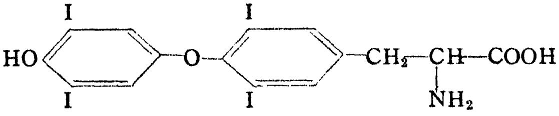
d. Histidine (β-imidazole-α-aminopropionic acid).



This amino acid was isolated in 1896. Histidine, arginine, and lysine are often known as the hexone bases, since they all contain six carbon atoms and an excess of basic amino groups over acidic carboxyl groups.

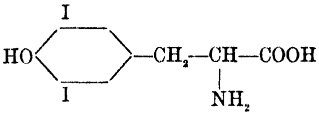
D. Other Amino Acids.

a. Thyroxine [β-(3,5,3′,5′-tetraiodo-4′-hydroxydiphenyl ether)-α-aminopropionic acid].



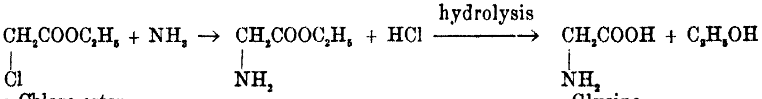
Thyroxine was isolated by Kendall in 1919. It is the only amino acid known to have the properties of a hormone. It occurs in a combined form in thyroglobulin, which is the chief protein of the thyroid gland. Thyroxine regulates the oxidative processes in the body. Kendall has estimated that the injection of one milligram of thyroxine will cause an increase in the carbon dioxide output of the body of approximately 400,000 milligrams.

b. Iodogorgoic acid (3,5-diiodotyrosine).



Iodogorgoic acid is closely related to thyroxine in structure. The ancient Greeks considered ground sponges to be specific remedies for goiter. The belief later was ridiculed until it was found that the protein of sponges contains 1.0 to 1.5 per cent of iodine as the amino acid, iodogorgoic acid. If the iodine atoms in iodogorgoic acid are replaced by bromine atoms, an amino acid, called dibromotyrosine, is obtained. It has been found to be a constituent of corals.

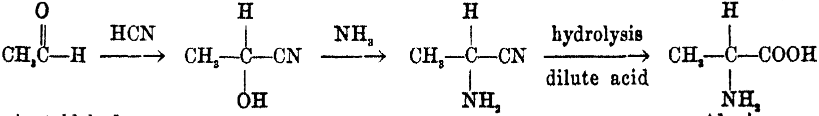
Synthesis of Amino Acids.—The structure of an amino acid is not proved until it has been synthesized in the laboratory. Two methods available for such syntheses will be considered. One of these is the reaction of an α-chloro-ester with ammonia.



$$\underset{\substack{|\\ \mathrm{Cl}}}{\mathrm{CH_2}}\mathrm{COOC_2H_5} + \mathrm{NH_3} \rightarrow \underset{\substack{|\\ \mathrm{NH_2}}}{\mathrm{CH_2}}\mathrm{COOC_2H_5} + \mathrm{HCl} \xrightarrow{\text{hydrolysis}} \underset{\substack{|\\ \mathrm{NH_2}}}{\mathrm{CH_2}}\mathrm{COOH} + \mathrm{C_2H_5OH}$$

α-Chloro-ester Glycine

Another method of synthesizing amino acids involves the action of an aldehyde and hydrocyanic acid (Strecker reaction).

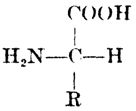


$$\mathrm{CH_3}\overset{\substack{\mathrm{O}\\ \|}}{\mathrm{C}}\mathrm{-H} \xrightarrow{\mathrm{HCN}} \mathrm{CH_3-}\underset{\substack{|\\ \mathrm{OH}}}{\overset{\substack{\mathrm{H}\\ |}}{\mathrm{C}}}\mathrm{-CN} \xrightarrow{\mathrm{NH_3}} \mathrm{CH_3-}\underset{\substack{|\\ \mathrm{NH_2}}}{\overset{\substack{\mathrm{H}\\ |}}{\mathrm{C}}}\mathrm{-CN} \xrightarrow[\text{dilute acid}]{\text{hydrolysis}} \mathrm{CH_3-}\underset{\substack{|\\ \mathrm{NH_2}}}{\overset{\substack{\mathrm{H}\\ |}}{\mathrm{C}}}\mathrm{-COOH}$$

Acetaldehyde Alanine

Physical Properties of the Amino Acids.—The amino acids are white, crystalline solids. Almost all of them except tyrosine and cystine are water soluble. Proline and hydroxyproline are the only amino acids that are soluble in alcohol. Some of the amino acids are sweet, many are tasteless, and some are bitter.

Stereoisomerism and Optical Activity of the Amino Acids.—As was true in the case of the sugars, almost all of the amino acids contain at least one asymmetric carbon atom; therefore, they exhibit stereoisomerism. The prefixes D- and L- are used before the names of the amino acids to denote the spatial configuration of the asymmetric α-carbon atom in the amino acid. The structural formulas of the amino acids belonging to the L-family can be depicted in the usual manner with the amino group on the left of the α-carbon atom, while those with the amino group shown to the right belong to the D-family.*



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H_2N{-}C{-}H} \\ | \\ \mathrm{R} \end{array}$$

Type formula for an L-amino acid

When it is desired to show the direction of optical rotation of an amino acid, a + (dextrorotatory) or a − (levorotatory) sign is placed before the name of the acid. Most of the naturally occurring amino acids are levorotatory (−), but some are dextrorotatory (+). The amino acids obtained by synthetic means are composed of equal amounts of the dextro- and levo-isomers and are, consequently, optically inactive. Special methods of resolution (discussed on page 256) must be used to separate the optically active forms of amino acid from this racemic mixture.

Essential Amino Acids.—Certain amino acids have been found indispensable for protein synthesis in the body; that is, unless these acids are present in the diet, protein synthesis is blocked. First conclusive results on this subject were offered by Rose and his co-workers. One of the techniques

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*Older literature used *l*- and *d*- instead of L- and D- for depicting spatial arrangement of the α-amino group. The change to L- and D- is made in accordance with the 1947 recommendations of the A.C.S. committee on chemical nomenclature.

they used was to feed young rats a diet containing the necessary carbohydrate and fat plus a mixture of pure amino acids to supply the protein. Thus it was possible by varying the diet to discover which of the amino acids were the indispensable ones. Their criteria for "essentiality" consisted in maintenance of a normal growth rate. They concluded that the following amino acids were essential:

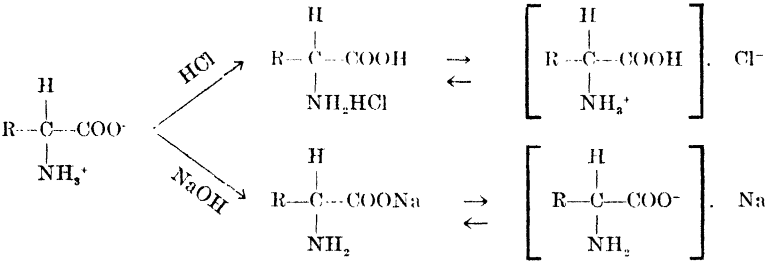
Arginine
Valine
Leucine
Isoleucine
Threonine
Phenylalanine
Tryptophan
Methionine
Lysine
Histidine

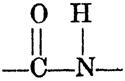
At one time, cystine and tyrosine also were thought to be essential. Experimental results have shown, however, that tyrosine can be omitted from the diet if sufficient phenylalanine is fed. Likewise, cystine need not be supplied by the diet if sufficient methionine is fed.

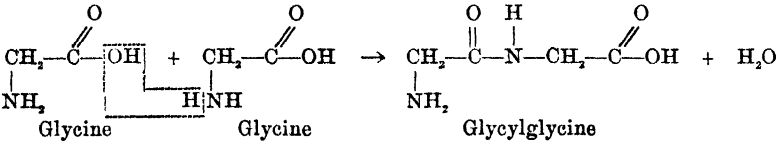
Care must be taken in applying too literally the results obtained on experimental animals to human nutrition. Obviously, the cost and labor involved in the preparation of sufficient amounts of amino acids to be used in extensive experiments on humans is prohibitive. Recent results on a limited number of humans, however, seem to confirm the list of essential amino acids proposed by Rose although there is some doubt about the essentiality of histidine. Rose and others have used nitrogen balance studies of human subjects as a criterion for essentiality of the amino acids.

Animals that are fed a diet lacking or low in the essential amino acids fail to grow normally. Thus, in the final analysis, the quality of the protein in the diet depends on the amino acid content of the foodstuff. Certain proteins are classed as "incomplete proteins," because they are lacking in some of the essential amino acids. Gelatin lacks tryptophan and tyrosine, and is low in histidine; gliaden of wheat has been shown to be deficient in lysine; zein of corn is practically devoid of lysine and tryptophan. None of these proteins will support growth if they are the only source of protein in the diet. Vegetable proteins, as a group, are often incomplete proteins, although soybean protein and pumpkin seed globulin are exceptions. As a rule, it is unsafe to allow them to constitute the sole source of protein in the diet without supplementing them with other proteins that contain adequate quantities of the missing amino acids.

Chemical Properties of the Amino Acids.—The amino acids are amphoteric in nature; that is, they are able to form salts with either acids or bases. Such a property is best accounted for by the *zwitter ion* (hybrid or hermaphrodite ion) theory. Amino acids in aqueous solution exist chiefly in the form of zwitter ions. They carry both a positive and a negative charge; thus, they can react both with acids and with bases.

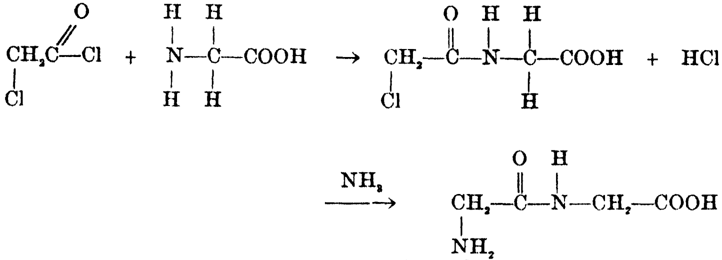


Since amino acids contain the acidic carboxyl group and the basic amino group, it would be expected that they would react with each other with the elimination of water to form a  $\overset{\overset{O}{\|}}{-C}-\overset{\overset{H}{|}}{N}-$ type of linkage. Evidently this takes place in living processes, for the preponderant type of coupling of amino acids in proteins is by this linkage, termed the *peptide linkage.* The formation of the peptide linkage by the reaction of two molecules of glycine can be represented as follows:



More than two amino acids can be linked together in this fashion, and the acids need not necessarily be of the same kind.

Long-chain polypeptides cannot be prepared in the laboratory by the direct reaction of amino acids. Emil Fischer, by indirect methods, was able to carry out the laboratory synthesis of high-molecular weight polypeptides. He succeeded in linking 18 amino acids together with polypeptide linkages by the reaction of the α-halogen-substituted carboxylic acid chloride with an amino acid. The halogen of the resulting compound is replaced by an amino group when the compound is treated with ammonia.



$$CH_2Cl{-}C(=O){-}Cl + H_2N{-}CH_2{-}COOH \rightarrow CH_2Cl{-}C(=O){-}NH{-}CH_2{-}COOH + HCl \xrightarrow{NH_3} CH_2(NH_2){-}C(=O){-}NH{-}CH_2{-}COOH$$

Glycylglycine

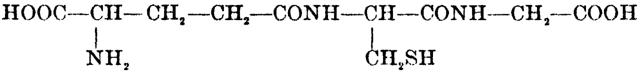
The foregoing equation illustrates the synthesis of a dipeptide. If a more complex polypeptide is desired, the acid chloride is formed from the product resulting from the first step in the reaction. The acid chloride then is reacted further with an amino acid, and the reaction is continued in this fashion until the desired length of chain is obtained. The product finally is treated with ammonia, which replaces the chlorine atom by an amino group to give the polypeptide.

Other methods of synthesizing polypeptides also have been developed, and are described in more advanced organic chemistry textbooks. The high-molecular weight polypeptides are similar in a number of respects to proteins. They show the biuret reaction (see page 572) typical of all proteins; they can be salted out by neutral salts in the same manner as the proteins; and they are hydrolyzed by the peptidases of the intestinal mucosa.

A recent announcement that may have far-reaching consequences in the field of protein chemistry both from theoretical and practical standpoints is that of Woodward, one of the scientists who synthesized quinine. He reported the polymerization of anhydrides of N-carboxy-α-amino acids to substances with molecular weights in the range of 1 to 1.5 million. The polymers were cast into tough, mechanically stable films, and also were drawn into fibers. The polymerization was carried out at room temperature. Thus he prepared a synthetic material resembling natural proteins from derivatives of α-amino acids.

Certain investigators believe that linkages other than the peptide linkage also may be present in proteins. The bulk of the experimental work, however, seems to confirm the idea that the principal linkage in the protein molecule is the peptide linkage.

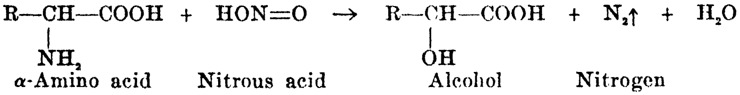
The tripeptide glutathione is of special interest, for it is present in most cells, where apparently it serves as a hydrogen carrier. The sulfhydryl group (—SH) in the molecule easily is oxidized to the disulfide form (—S—S—), and this form easily can be reduced back to the —SH form. The reaction is similar to the interconversion of cysteine and cystine.



$$HOOC—\underset{NH_2}{\underset{|}{CH}}—CH_2—CH_2—CONH—\underset{CH_2SH}{\underset{|}{CH}}—CONH—CH_2—COOH$$

Glutathione
(γ-Glutamyl-cysteinyl-glycine)

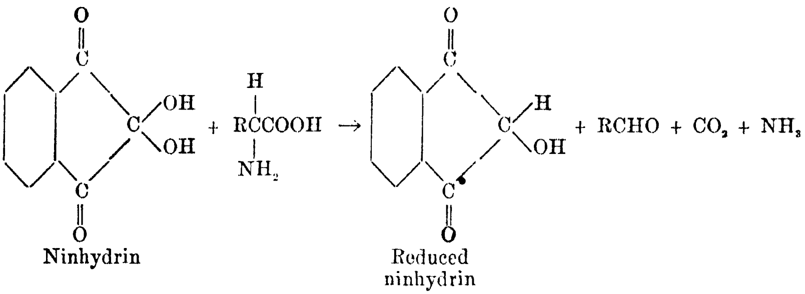
Reaction with nitrous acid. The amino acids react with nitrous acid to form an alcohol and elementary nitrogen.



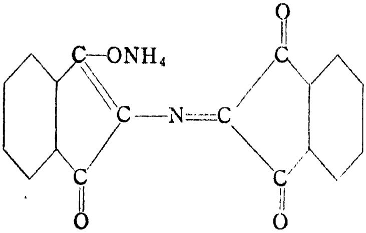
$$\underset{\alpha\text{-Amino acid}}{R—\underset{NH_2}{\underset{|}{CH}}—COOH} + \underset{\text{Nitrous acid}}{HON{=}O} \rightarrow \underset{\text{Alcohol}}{R—\underset{OH}{\underset{|}{CH}}—COOH} + \underset{\text{Nitrogen}}{N_2\uparrow} + H_2O$$

The Van Slyke method for the determination of α-amino nitrogen is based on this reaction. The method can be used successfully for following the rate of protein hydrolysis, for, as the protein is hydrolyzed (broken down into free amino acids), more α-amino groups, which react with the nitrous acid, are liberated.

Reaction with ninhydrin (triketohydrindene hydrate). Van Slyke and his co-workers published a paper late in 1941 describing a procedure for the quantitative determination of free amino acids by the use of ninhydrin. The method depends on the measurement of carbon dioxide formed by the reaction between free amino acids and ninhydrin.



If the reaction is carried out above pH 4, the ammonia condenses with ninhydrin and its reduction product to give a compound with a blue to purple color. It has the following structural formula:



The quantitative method described by Van Slyke is uniquely specific for free amino acids in that it requires the presence, in the free, uncombined state, of both the carboxyl and the neighboring NH_2 or $—NH—CH_2$ group. Peptides (other than glutathione) do not evolve carbon dioxide under the conditions of the determination, and only 0.03 per cent of the total nitrogen of such proteins as casein is estimated by the method. Hence, the method is capable of determining free amino acids in the presence of proteins and peptides.

An acidity of pH 2.5 was found most suitable for the determination of free amino acids in a mixture such as is obtained by the partial hydrolysis of a protein.

The carbon dioxide evolved in the reaction can be determined by a titration method using barium hydroxide as an absorbent for the carbon dioxide.

The method appears to be quicker and to require less skill to perform than the older Van Slyke α-amino nitrogen method.

Reaction with formaldehyde. The amino acids react with formaldehyde to mask the amino group so that the carboxyl group acts as a simple organic acid. Hence the amino acid is no longer amphoteric but reacts only as an acid and thus it is possible to determine the "free carboxyl groups" by titration with a standardized solution of sodium hydroxide. The method is known as *Sörensen's titration,* and can be used in following the hydrolysis of proteins, for as the hydrolysis proceeds, more carboxyl, as well as amino, groups are set free.

Microbiological Assay of Amino Acids.—In the last decade the microbiological assay method for the determination of amino acids has been developed. Microorganisms require for their growth many of those substances that are now known to be essential constituents of all living cells; therefore, their growth can be used as a measurement of certain of these specific substances in a carefully planned medium. The sample to be analyzed is run at a series of concentrations with controls of the pure substance to be determined run at the same dilutions. Lactic acid bacteria and mutant cultures of *Neurspora crassa* and of *Escherichia coli* have been used for this type of investigation. When lactic acid bacteria are used, their growth can be measured either by the number of organisms present in the medium or more commonly by titration of the acid produced as a by-product of growth.

The microbiological assay method has certain advantages over other methods used for determining amino acids in proteins. No tedious and laborious separations are necessary as in many types of protein analysis; the method requires only simple laboratory equipment readily available, and it requires only small quantities of material. The results agree well with the older tested methods.

Proteins

Protein Classification.—The criteria usually used for identifying compounds, such as boiling point, melting point, molecular weight, crystalline form, etc., are of little use in characterizing proteins, for in so many cases these characteristics are not definitely known. Protein classification, therefore, depends chiefly on differences in solubility and to a limited extent on constitution. The three large divisions are: (A) simple proteins, (B) conjugated proteins, and (C) derived proteins.

(A) **Simple Proteins.**—*The simple proteins yield chiefly amino acids or their derivatives on hydrolysis.* They are divided into the following seven subgroups:

1. *Albumins.* The albumins are soluble in water and dilute salt solutions, and are coagulated by heat. Typical examples are egg albumin, lactalbumin from milk, serum albumin from blood serum, and leucosin from wheat.

2. *Globulins.* The globulins are insoluble in water, but are soluble in dilute solutions of neutral salts, as, for example, 5 per cent sodium chloride. In general, they are coagulated by heat. Examples of this class are serum globulin from blood serum, fibrinogen from blood plasma, edestin from hemp seed, and legumin from legume seeds. The vegetable globulins form the major portion of the protein of most seeds except cereals, and are among the most common protein reserves.

3. *Glutelins.* The glutelins are insoluble in water, neutral salt solutions, and alcohol, but will dissolve in dilute acids and alkalies. They represent a small group of proteins that are exclusively of plant origin. Characteristic glutelins are glutenin from wheat endosperm, and oryzenin from rice.

4. *Prolamines.* The prolamines are insoluble in water, absolute alcohol, and other neutral solvents, but are soluble in 70 to 80 per cent alcohol. The proteins of cereal grains are composed largely of prolamines. With the exception of lactoprolamine from milk, prolamines are obtained only from cereal grains. The name itself is derived from the fact that these proteins contain a high percentage of the amino acid proline.

Examples of typical prolamines are gliadin from wheat and rye, zein from corn endosperm, and hordein from barley endosperm.

If water is added to wheat flour and the dough thus formed is kneaded under a stream of water to wash out the starch, the yellow, elastic mass that remains is known as crude *gluten.* The two proteins, gliadin and glutenin, can be separated from this material if desired. Both the quantity and the quality of this crude gluten determine the baking quality of a flour. A number of years ago, the quality, and accordingly the price, of wheat was based upon the amount of crude gluten obtained from a given weight of grain. At the present time, cereal chemists base their judgment of the quality of wheat on the nitrogen content of the wheat as determined by the Kjeldahl method and upon experimental baking tests on the finished flour. In the routine buying of wheat by flour mills, the nitrogen content is often the only criterion used for judging wheat quality.

Many mechanical devices have been invented for testing dough with the object of ascertaining its suitability for baking, especially for breadmaking. These instruments, such as the farinograph and the extensometer, test the tensile strength of the dough. A "strong" flour, in the terminology of the cereal chemist, is one in which the gluten has sufficient tensile strength so that it will give the desired volume in a loaf of bread. By the same standards, a "weak" flour tends to give a flat loaf or small volume. Hard winter and spring wheats tend to give strong flours; whereas soft wheats give a weak flour, which is better adapted to the making of pastry and cakes than of bread. Soft wheats are grown in warm climates, while hard wheats are grown farther north.

5. *Albuminoids.* The albuminoids sometimes are called *scleroproteins.* They are insoluble in all the solvents mentioned thus far. It is questionable whether or not they are soluble in any solvent without being altered chemically. Examples of albuminoids are keratins from such epidermal tissue as horns, hoofs, hair, hides, and fingernails; collagen from tendons; elastin from ligaments; and fibroin from silk. Gelatin usually

is included in this group, since it is obtained from hoofs and hides, although its physical properties are not characteristic of the true albuminoids.

6. *Histones.* The histones are soluble in water, dilute acids, and strong bases, but are precipitated from water by ammonium hydroxide. Some of them are not coagulated by heat. The chief source of histones is glandular tissue. Typical examples are thymus histone from the thymus gland and globin* from hemoglobin. Histones are basic proteins, but not to the same degree as are the protamines. Histones give many amino acids on hydrolysis, but the basic amino acids (histidine, lysine, and arginine) predominate.

7. *Protamines.* Protamines possess strongly basic properties. They are soluble in water and ammonia, and are not coagulated by heat. They are the simplest of all naturally occurring proteins. Some investigators regard them as large polypeptides. On hydrolysis they yield only a few amino acids, of which arginine predominates. The protamines have been obtained mainly from the sperm of fish. Examples are salmine from salmon sperm, which contains 88 per cent arginine, and sturine from sturgeon sperm. Protamines are the only proteins that do not contain combined sulfur.

(B) **Conjugated Proteins.**—Conjugated or compound proteins are substances that yield a simple protein plus a nonprotein, or prosthetic, group on hydrolysis.

1. *Phosphoproteins.* The prosthetic group in this class of conjugated proteins is phosphoric acid, which is assumed to be in combination by an ester linkage with the hydroxyl groups in hydroxy amino acids. Examples of phosphoproteins are casein from milk and vitellin from egg yolk.

2. *Glycoproteins.* The additional group in glycoproteins is a carbohydrate. Mucoids obtained from egg white, tendons, cartilage, and walls of the blood vessels; and mucins from

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*It has been suggested that globins be classified as a separate group since they differ from histones in isoelectric point and amino acid composition. Histones contain high percentages of arginine and isoleucine but only traces of tryptophan. Globins, on the other hand, contain average quantities of arginine and tryptophan and are unusual in their high content of histidine and deficiency of isoleucine. The solubility behavior of histones and globulins, however, are similar.

saliva and egg white are examples of glycoproteins. Certain of the mucins contain as much as 15 per cent carbohydrate, which is thought to be largely mannose and galactose. The protein making up most of the structure of the jellyfish is a glycoprotein.

3. *Nucleoproteins.*—Nucleoproteins are compounds of nucleic acid and basic proteins, usually a histone or a protamine. They make up the greater part of the chromatin material of cell nuclei, chromatin being the structural material of chromosomes. Nucleoproteins are present in all living cells that contain nuclei, and some recent evidence indicates that nucleoproteins also may be present in cytoplasm (protoplasm outside of nucleus). Wheat embryos serve as an important source of nucleoproteins. They also have been isolated from yeast cells and thymus gland.

The mode of linkage between the protein and the nucleic acid is not definitely known. The two can be separated easily; and when nucleic acid is decomposed, it yields phosphoric acid, a carbohydrate, and pyrimidine and purine bases. The sugar from the nucleic acids of yeast and other plants is ribose, while that from thymus nucleic acid is desoxyribose.

4. *Chromoproteins.* As the name chromoprotein suggests, the prosthetic group in this class of proteins is colored. A familiar example is the hemoglobin of blood. The colored prosthetic group is an iron-containing compound called *heme.* The hemoglobin molecule is about 96 per cent globin and 4 per cent heme. (For a more detailed discussion of the chemistry and function of hemoglobin see page 590.)

Another chromoprotein is melanin, the pigment in black feathers, wool, and hair. It also is the pigment in human skin responsible for the color of freckles and sun tan. It is present in much higher concentration in Negro skin. It has been shown that melanin absorbs ultraviolet light so that it functions to protect the lower layers of the skin from the deleterious effect of overexposure to this form of radiant energy.

The respiratory pigment of oysters, mollusks, lobsters, and other crustacea is hemocyanin, in which copper has replaced the iron of hemoglobin. The oxygenated respiratory pigment of these species is blue instead of red.

Visual purple of the retina of the eye is a chromoprotein in which the prosthetic group is vitamin A or a closely related substance. If the diet is deficient in vitamin A (see page 727), the normal amount of visual purple fails to develop, and a nutritional type of "night blindness" results.

5. *Lecithoproteins.* In these proteins the conjugated group is lecithin or another phospholipid. Thromboplastin (often termed thrombokinase) is an example of this class. It is one of the substances necessary for the coagulation of blood. It occurs most abundantly in lung tissue where perhaps it functions to prevent hemorrhages in the many fine capillaries.

(C) **Derived Proteins.**—These proteins do not occur naturally. The term includes those proteins that have been changed in their properties by the action of physical or chemical agents. Derived proteins can be divided into two groups: (1) primary derived proteins, in which there is no change in molecular weight or particle size; and (2) secondary derived proteins, which are products of smaller molecular weight or size than the original protein.

1. *Primary derived proteins.* The characteristic solubility behavior of native proteins is changed by the action of a number of agents. Coagulated egg albumin is a familiar example of the effect of *heat* on a protein. The irradiation of an aqueous solution of egg albumin with ultraviolet radiant energy also will coagulate the protein. Another example of the effect of radiant energy on proteins is the use of *x-rays* to destroy cancer cells. One reason for the destruction of the cancer cells by x-rays is the coagulation or denaturation of the protein. Fortunately, the protein of cancer cells is more sensitive to the action of the x-rays than is that of the normal tissue cells.

Ultrasonic waves have been shown to coagulate proteins. They are waves of very high frequency that are inaudible to human ears. The action of *acid* on globulins causes them to lose their solubility in dilute salt solutions. The proteins thus obtained are termed *proteans.* The transformation of edestin to edestan by the action of acid is an example of this transformation. Proteins also are denatured by the action of detergents, such as the sulfated alcohols (like Dreft). Another method of preparing derived proteins is by *surface denaturation.* This can be brought about by vigorous shaking, foaming, or the passing of a current of inert gas through a protein solution.

2. *Secondary derived proteins.* Secondary derived proteins are the hydrolytic products of proteins; that is, they are substances of smaller molecular weight than the original protein. The hydrolysis of proteins can be depicted as:

Protein → Proteoses → Peptones → Peptides → Amino acids

The proteoses can be precipitated by saturating the solution with ammonium sulfate. Peptones will not precipitate when the solution is saturated with ammonium sulfate. Essentially, they are mixtures of polypeptides of unknown composition. The peptides contain only a few amino acids linked together, and cannot be precipitated by ammonium sulfate. Precipitation of the protein split products is dependent on the size of the protein fragments. The larger the fragment, the lower the concentration of ammonium sulfate required to precipitate it.

The foregoing classification of proteins is useful for general purposes, but it is far from satisfactory. For example, globulins are defined as proteins soluble in dilute solutions of neutral salts. Gortner and co-workers have raised the pertinent question: What salts and what concentrations? They found that with regard to the effectiveness of the dispersing (peptizing) action of neutral inorganic salts, a *lyotropic series* exists. The order of effectiveness of salts as dispersing agents for cereal proteins was found to be:

$$KF < KCl < KBr < KI$$

However, any changes in the protein classification would cause much confusion in the chemical literature and would destroy many of the benefits resulting from the existing classification.

Methods of Isolating Proteins.—If it is desired to isolate the different classes of proteins from a material, a number of procedures may be followed. For example, in the case of seeds, the proteins can be separated conveniently by proper treatment of the ground, dry material. The albumins are extracted with water, the globulins with 5 per cent sodium chloride, prolamines with 70 to 80 per cent alcohol, and the glutelins are extracted from the residue with dilute alkali. Different solutions of proteins thus are obtained, and it is then necessary to precipitate the proteins from the solutions.

To isolate the albumins from the aqueous solution, sufficient ammonium sulfate is added to saturate the solution, whereupon the albumins precipitate. The solution containing the globulins is mixed with an equal volume of a saturated solution of ammonium sulfate, and the globulins precipitate. The globulins also can be isolated by pouring the salt solution into a cellophane bag and dialyzing against running water. The process of dialysis consists in a ''straining or sieving out'' of the protein molecules. The inorganic ions are diffusible, and pass through the cellophane bag, whereas the large protein molecules are retained. After the major portion of the inorganic salts has been removed by dialysis against running water, the remainder can be removed by electrodialysis. This process is carried out in an apparatus with three compartments. The protein solution is placed in the middle one, which is separated from the others by membranes of parchment or cellophane. Usually an electrode of carbon or platinum is placed in each of the end compartments, and a direct current under a potential of 110 to 250 volts is applied. Under the influence of this high voltage, the inorganic ions migrate through the cellophane or parchment membranes to the end compartments. Water is kept circulating through the electrode compartments in order to keep the protein solution cool and to carry away the inorganic ions. When the salts have been removed in this way, the globulins precipitate.

The prolamines are precipitated by diluting the alcoholic solution with water. The glutelins are separated by the addition of acid to the point of maximum precipitation.

Such a procedure is a typical process for the isolation of the simple proteins from the reserve proteins in plant seeds. For the isolation of proteins from fresh plant material or animal tissue, freezing often is used as a means of breaking the cell structure and rendering the protein material available for extraction with solvents. The material can be frozen at a slow rate and allowed to thaw, and the proteins can be separated by methods already described or, for the isolation of proteins other than those found in seeds, by methods described in laboratory manuals of biochemistry.

An alternate method of treating fresh material is to freeze it and then grind it in the frozen state, the protein being extracted after the ground material thaws. The proteins that are in solution are separated from the undissolved residue by pressing through cloth, centrifuging, and, in some cases, by filtration, although frequently the pores of the filter paper clog and filtration is very slow.

The methods that have been described yield a protein in the moist state, which soon undergoes bacterial putrefaction unless it is kept at a low temperature or in the presence of some preservative. It often is desirable to obtain the protein in a dry state. To accomplish this without denaturing or altering the protein has been, and still is, one of the most perplexing problems of the protein chemist. One method of obtaining a dry protein that is altered only slightly in character is to precipitate it with cold (–5° C.) 95 per cent alcohol; filter it on a hardened filter paper, using reduced pressure; and wash it with absolute alcohol and absolute ether. The drying process is completed in a desiccator over concentrated sulfuric acid.

Proteins sometimes have been obtained in the dry state by precipitation with acetone, washing with absolute acetone, and drying in a desiccator over sulfuric acid.

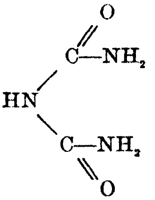
Still another method of obtaining a dry protein, and a method claimed to cause the least denaturation, is the lyophilization method. This method is carried out by first freezing the purified protein in a suitable container, such as a round-bottomed flask. The container then is connected to an efficient mechanical vacuum pump and the vapors passed through a condenser surrounded by ether and dry ice (solid CO_2). The water vapor thus is frozen out as it sublimes from the protein material. By this procedure the protein is obtained as a dry, powdery material that has never been exposed to temperatures that would denature it.

Precipitation of Proteins.—Often it is desirable to separate proteins from a solution that contains other materials. This usually is accomplished by means of protein precipitating reagents. For example, in the analysis of a carbohydrate material, it may be necessary to remove protein before the analysis of the carbohydrate; or for the determination of the total protein content of a material, a method of separating the protein is necessary. Substances that are used to precipitate proteins are phosphotungstic acid, trichloroacetic acid, sulfosalicylic acid, picric acid, tannic acid, and salts of heavy metals, such as copper, mercury, or silver. These substances form insoluble complexes with the protein material, from which the protein can be recovered in some instances; in other cases (for example, if only the nitrogen content is to be determined), this step of obtaining the free protein is not necessary. The separation of proteins by means of these precipitating agents is not used if the material is to be used for physicochemical measurements, such as molecular weight determinations, since the proteins usually are modified by the action of the precipitating agents.

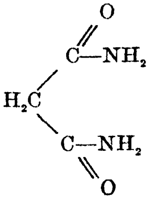
Color Reactions of the Proteins.—The color reactions given by proteins are dependent on certain types of linkage in the protein molecule, or on the presence of specific amino acids. Some of the tests are general for all proteins; others are specific for certain amino acids in the protein.

1. *Biuret test.* The test is carried out by adding 2 to 3 cc. of 20 per cent sodium hydroxide to an equal volume of the solution being tested. Then a few drops of 0.5 per cent copper sulfate solution are added. If protein is present, a blue or violet color develops. Smaller molecules, such as proteoses and peptones, yield a pink or pink-violet color. Free amino acids do not form a color; hence the biuret test can be used to determine the completeness of a protein hydrolysis.

The test is positive for compounds that contain acid amide groups in close proximity, such as in the peptide linkages in chains of amino acids. Such compounds as biuret (from whence the test derived its name) and malonamide give positive tests, since they, too, have amide groups close together in the molecule.



Biuret



Malonamide

2. *Xanthoproteic test.* Anyone who has spilled nitric acid on his skin has seen the xanthoproteic test. Proteins assume a yellow color in the presence of concentrated nitric acid. If an excess of sodium hydroxide is then added so that the solution becomes alkaline, the yellow color turns to orange. The test depends on the formation of nitrobenzene or dinitrobenzene derivatives from the benzene nuclei present in the protein. The test, therefore, is specific for tyrosine and tryptophan. Phenylalanine does not nitrate easily; therefore, ordinarily it does not take part in the reaction. Gelatin gives only a faint color when the xanthoproteic test is applied, because it is deficient in tyrosine and tryptophan.

3. *Millon's reaction.* Heating a protein solution in the presence of Millon's reagent (mercury dissolved in nitric acid) causes the protein to precipitate. This precipitate is white, but when it is heated, it becomes a brick-red color. The test depends on the presence of tyrosine. Proteins that do not contain this amino acid will not give the test. The test is not satisfactory when the solution contains large amounts of free chloride ion.

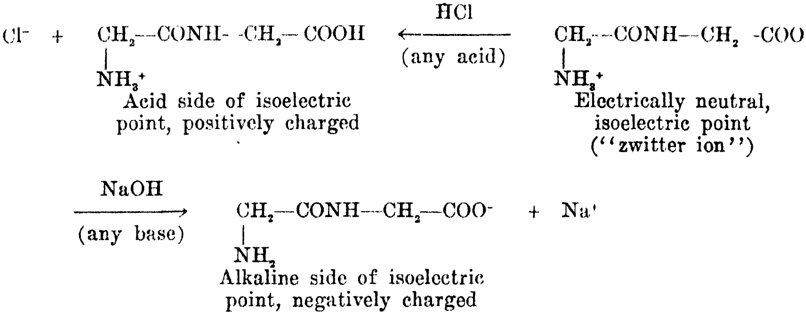
4. *Molisch test.* This reaction is used in testing for the presence of carbohydrate in a protein. To a small amount of protein solution are added a few drops of an alcoholic solution of α-naphthol. The mixture then is layered over concentrated sulfuric acid. If carbohydrate is present in the protein, a red-purple ring forms at the zone of contact of the two liquids.

5. *Sulfur test.* Proteins that have in their molecule sulfur-containing amino acids, such as cystine or methionine, are de-

composed with the formation of sodium sulfide when they are heated with sodium hydroxide. If a few drops of saturated lead acetate are added to such a solution, a brownish-black precipitate of lead sulfide will result.

Isoelectric Point of Proteins.—Like the amino acids, proteins are amphoteric in nature. The binding of acids and bases by proteins probably is due largely to the free amino and carboxyl groups, although the binding of acids and bases by adsorption, due to the colloidal nature of the protein, cannot be ruled out entirely as a factor.

Glycylglycine, the simplest dipeptide, will be used as an example of a type of reaction that proteins undergo with acids and bases. At a certain pH or zone of pH in the acid range, the peptide will carry a positive charge of electricity. Likewise, in the alkaline pH range, the peptide will possess a negative charge. At some intermediate pH there are an equivalent number of positive and negative charges, so that the peptide will be electrically neutral.



$$Cl^- + \underset{NH_3^+}{\underset{|}{CH_2}}-CONH-CH_2-COOH \xleftarrow[\text{(any acid)}]{HCl} \underset{NH_3^+}{\underset{|}{CH_2}}-CONH-CH_2-COO$$

Acid side of isoelectric point, positively charged

Electrically neutral, isoelectric point ("zwitter ion")

$$\xrightarrow[\text{(any base)}]{NaOH} \underset{NH_2}{\underset{|}{CH_2}}-CONH-CH_2-COO^- + Na^+$$

Alkaline side of isoelectric point, negatively charged

If electrodes connected to a source of direct current are immersed in a solution of the peptide in the acid range, the peptide will migrate toward the negative pole, or cathode, thus behaving as a cation. In the basic range the peptide possessing a negative charge will act as an anion and will migrate toward the anode, or positive pole. It is obvious that at some pH the peptide will be electrically neutral and there will be no tendency for it to migrate toward either pole. At this point, the peptide is said to be at its *isoelectric point.* The isoelectric point usually is defined in terms of pH.

The simplest dipeptide has been used in explaining isoelectric point, but the principles hold equally well for proteins, since the amino acids are linked mainly by the peptide linkage in these compounds. There are free amino and carboxyl groups in proteins.

Proteins are least soluble at their isoelectric point, and often are precipitated by adjusting their solution to the isoelectric pH with acid or alkali. Hydration (binding of water), as well as viscosity, is lowest at the isoelectric point.

Each protein has its own characteristic isoelectric point. A few examples are:

	pH
Egg albumin	4.6
Edestin	6.6
Hemoglobin	6.8
Casein	4.7
Gelatin	4.7
Histone	8.5

Use has been made of the difference in the isolectric points of insulin and of protamines in the treatment of diabetes with protamine insulinate. The isoelectric point of insulin is 5.3, that of protamines is about 12.2, while blood has a pH of about 7.38 to 7.40. Hence, protamines in the blood stream would be on the acid side of their isoelectric point, and, accordingly, would possess a positive charge. Insulin, on the other hand, would be on the alkaline side of its isoelectric point, and, consequently, would be negatively charged. A combination of one part protamine to ten parts insulin is used for injection, and at the pH of blood the two substances are attracted to each other because of their electrical charges. The insulin is absorbed slowly from this combination, and thus becomes available to the patient in small amounts over a relatively long period, which lessens the necessity for frequent injections of insulin.

Molecular Weight of Proteins.—It is an accepted fact that the proteins are large complex molecules. Several methods have been used in efforts to determine the molecular weight of proteins, but we shall consider only the ultracentrifuge method. A prominent worker in this field, and the one who introduced the technic, is T. Svedberg of Sweden. The protein solutions are centrifuged at a speed as great as 75,000 r.p.m., which corresponds to a centrifugal force of approximately 400,000 times gravity. The rate of sedimentation is determined photographically through quartz or glass windows in the casing of the ultracentrifuge. When a number of other physical constants are known, the molecular weight of the protein can be determined by a complicated series of calculations. Some of the molecular weights of various proteins determined by the ultracentrifuge technic are:

Tobacco mosaic virus	60,000,000
Gliadin	34,500
Hemoglobin (horse)	68,000
Serum albumin	70,000

Biological Reactions of the Proteins.—The variations possible in proteins can be appreciated if one thinks of them as different combinations of amino acids. If we were to assume that a protein is made up of 20 different amino acids, and that each acid occurred only once in the protein molecule, then there would be 24×10^{17} possible ways of combining these same amino acids into proteins differing only in their internal configurations. In truth, most proteins have a far greater molecular weight than a compound built of only 20 amino acids would have, and there are no proved rules limiting the number of times a certain amino acid can appear in a protein molecule; therefore, the number of combinations of amino acids possible for proteins is enormous. One of the wonders of nature is that particular proteins appear constantly to be synthesized by particular species from generation to generation. Thus, casein isolated now from cow's milk apparently is the same protein as casein isolated from cow's milk many years ago. Likewise, the chemical composition of egg albumin, and of countless numbers of other proteins, apparently always remains the same.

That there are important, if small, differences between proteins can be illustrated strikingly by injections of small amounts of foreign protein into the blood stream of animals. This is illustrated by the violent reaction known as *anaphylactic shock.* The phenomenon was discovered by Charles Richet, professor of physiology at the University of Paris. He was attempting to produce immunity in his experimental dogs to a certain toxic protein. He injected the dogs with a minute quantity of the protein with no visible effect on the animals. Two weeks later he injected a slightly larger dose. Instead of acquiring immunity by the second injection, the animals died. The physiological reaction now is known as anaphylactic shock. The first injection of protein evidently brings about some change in the animal's system to "sensitize" him to a second injection. The time interval between the sensitizing dose and the shock dose can vary widely (one to six weeks), depending on experimental conditions, and, in particular, on the size of the sensitizing dose. In general, the larger the sensitizing dose, the longer will be the interval required for a reaction when the second dose is given.

If small amounts of foreign protein are injected at rather frequent intervals (three- or four-day intervals), anaphylactic shock does not result, but the organism gradually builds up a tolerance toward increasingly larger amounts of the foreign protein. Such a process is involved in the "desensitization" procedure often used in treating persons known to be sensitive to certain proteins.

The physiological symptoms of allergies (abnormal sensitivity to certain proteins) can be manifested in a variety of ways. In some it is evidenced by painful swellings of parts of the body; in others the muscles of the bronchioles contract so that breathing becomes difficult and typical asthma results. In other persons the allergy manifests itself in migraine headaches or excessive watering of the nasal ducts.

Food allergies are, perhaps, the most common type. Proteins from wheat, egg, and milk are the three most frequent offenders, but are by no means the sole cause of food allergy. From the different cases on record, the list could be extended to include almost every known food. Some persons are allergic to such substances as cat's fur, feathers, kapok, dust, metals, certain drugs, cold, and other physical and biochemical agencies.

Industrial Uses of Proteins.—In addition to their great biological importance, proteins, as abundant natural materials, have many important industrial uses. For example, casein, obtained from skimmed milk by coagulation with the enzyme rennet, is used as a plastic. Many types of buttons and combs are made from this material. The casein obtained by adding acid to skim milk is used for the manufacture of cold water paints, for glue, as a paper coating, and even for textile fibers. Aralac is a casein-type fiber. These fibers have a resiliency resembling wool, and it is thought they have a promising future.

Fibers have been made from protein-detergent complexes using egg white or chicken feather keratin as the source of protein. Such fibers have a high tensile strength, and their development points to the possible future use of these and other waste protein products as a source of commercial fibers.

Not only are animal proteins used industrially now, but also proteins from vegetable origin. Soybean proteins have been used for sizing and coating paper and in the manufacture of water paints. During World War II substantial amounts of soybean proteins went into the production of a fire extinguisher mixture where it provided a heavy durable foam. Zein from corn was much used during the war in combination with rosin as a shellac replacement. Peanut protein, zein, and soybean protein are all being investigated as potential sources of textile fibers. They show promise of being equal to the casein fibers now being produced.

Study Questions

1. Define proteins. What is the chief function of this class of foodstuff in the body?
2. What is the usual nitrogen content of proteins? Describe the Kjeldahl method for the analysis of nitrogen-containing material.
3. What are three methods of obtaining amino acids from proteins?
4. For your own convenience in learning the formulas of the amino acids, construct a compact tabulation of the various classes of amino acids and cite examples of each class.

5. What is the formula for the simplest amino acid? What is the only amino acid that is known to contain a tertiary carbon atom?
6. What criteria must be fulfilled before an amino acid is considered definitely to be a product of protein hydrolysis?
7. What amino acid is found to the extent of about 14 per cent in human hair?
8. What is the name of the sulfur linkage in cysteine? In cystine?
9. What are the two alcohol-soluble amino acids?
10. What are the hexone bases? Why are they designated as such?
11. What is the only known amino acid that acts as a hormone?
12. Write equations to illustrate two possible methods of synthesizing amino acids.
13. List the essential amino acids.
14. What are ''incomplete proteins''? Give some examples and tell why these should not be used as a sole source of protein in the diet.
15. Why are the proteins amphoteric?
16. What is the peptide linkage? Write a formula for a tripeptide and indicate the peptide linkages.
17. Describe a method of synthesizing long-chain polypeptides.
18. Write an equation to represent the Van Slyke method for the determination of α-amino nitrogen.
19. What is the chief basis for the classification of proteins? In tabular form, list the types of simple, conjugated, and derived proteins, giving the essential characteristics and examples of each kind of protein.
20. What relationship does gluten have to flour quality? What is the difference between a ''strong'' flour and a ''weak'' flour?
21. What are the hydrolytic products of proteins in the order of decreasing molecular weight?
22. Describe several methods by which different classes of proteins might be isolated from a material.
23. What chemical reagents might be used as protein precipitants?
24. Describe the biuret test. What compounds other than proteins give a positive biuret test?
25. A positive xanthoproteic test shows that what amino acids are present in the protein-containing material?
26. What is the name of the test used for testing for the presence of carbohydrates in a protein? What is the active chemical reagent used in making the test?
27. What are the characteristics of a protein at its isoelectric point?
28. Why is protamine insulin more slowly absorbed by the body than free insulin?
29. What is meant by the term *biological specificity?*
30. What is the cause of an anaphylactic shock? Why do not allergic patients exhibit the symptoms of anaphylactic shock during a series of ''desensitization'' treatments?

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PART III

BIOLOGICAL CHEMISTRY

CHAPTER XXII

ENZYMES

Introduction.—Enzymes are organic substances that act as catalysts for most of the metabolic reactions of plant and animal tissues. They are made by living cells, but cells are not required for their activity; that is, enzymes are active catalysts even when they have been separated completely from organized tissue.

The substance undergoing change in the presence of an enzyme is known as the *substrate,* and the products formed as a result of the reaction are called *end products.* For example, in the presence of a *dipeptidase* (an enzyme), *dipeptides* (the substrate) are hydrolyzed to *amino acids* (the end products).

Most, if not all, the reactions catalyzed by enzymes are reversible. The hydrolysis of hexose phosphate, which is catalyzed by the enzyme phosphatase, may be taken as an example of this type of reaction.

$$\text{Hexose phosphate} + H_2O \xrightleftharpoons{\text{(phosphatase)}} \text{Hexose} + H_3PO_4$$

If hexose phosphate and water are mixed with a solution of the enzyme, the reaction proceeds to the right until a certain percentage of the hexose phosphate has been hydrolyzed. This reaction is catalyzed (accelerated) by the phosphatase. However, the phosphatase also accelerates the reverse reaction (formation of hexose phosphate from hexose and phosphoric acid). At first the reaction to the right is rapid, and the reaction to the left is slow. As time goes on, the concentrations of hexose and phosphoric acid increase, and the reaction to the left becomes faster, since there is more chance that molecules capable of reaction will come in contact with the enzyme and with each other. After a time, the reaction proceeds in both directions at the same rate, and no further change in concentrations then can be detected by ordinary chemical procedures. When this steady state is reached, the reaction is said to have reached its *equilibrium point.*

Many careful studies have demonstrated that *enzymes do not change the equilibrium points of reactions.* They simply accelerate the reaction in both directions, and the equilibrium point is reached more quickly than would be possible in the absence of the enzyme. It follows from this that *the same enzyme that catalyzes the breakdown of a substrate also will catalyze its formation under the proper conditions.* For example, if hexose phosphate is dissolved in a solution containing phosphatase, the principal detectable chemical change will be the hydrolysis of the hexose phosphate, with the simultaneous formation of free hexose and phosphoric acid. However, if free hexose and phosphoric acid are dissolved in a solution of the same enzyme (phosphatase), hexose phosphate will be formed. The relative amount of each substance present when a steady state is reached will depend on the equilibrium point of the reaction.

Nomenclature.—The modern names of enzymes are formulated by adding the ending *ase* to a prefix derived from the name of the substrate. Thus, protein*ases* catalyze the hydrolysis of proteins; lip*ases* catalyze the hydrolysis of lipids; and malt*ase* catalyzes the hydrolysis of maltose. Older chemists used the suffix *in* for names of enzymes. Many of these older names (ptyalin, rennin, pepsin, trypsin, steapsin, amylopsin, erepsin, cathepsin) still are used.

Classification.—In general, enzymes catalyze two major types of reaction: *hydrolysis* and *oxidation-reduction.* A brief list of the more important types of enzyme follows:

I. **Hydrolases.** These are the enzymes that catalyze hydrolytic reactions.
   A. *Esterases.* These enzymes catalyze the hydrolysis of esters with the formation of alcohols and acids.
      1. *Lipases* catalyze the hydrolysis of lipids.
      2. *Phosphatases* catalyze the hydrolysis of phosphoric acid esters.

B. *Carbohydrases.* These are enzymes that catalyze the hydrolysis of carbohydrates.
   1. *Amylases* catalyze the hydrolysis of starch. (*Amylum* is the Latin term for starch.)
   2. *Sucrase* catalyzes the conversion of sucrose to glucose and fructose.
   3. *Maltase* catalyzes the conversion of maltose to glucose.
   4. *Lactase* catalyzes the conversion of lactose to glucose and galactose.

C. *Proteases.* These enzymes catalyze the hydrolysis of proteins and derived proteins.
   1. *Proteinases* catalyze the hydrolysis of proteins.
   2. *Polypeptidases* catalyze the hydrolysis of polypeptides.
   3. *Dipeptidases* catalyze the hydrolysis of dipeptides.

D. *Desamidases.* These enzymes catalyze the hydrolytic cleavage of —C—N— linkages that are not in proteins or peptides.
   1. *Urease* catalyzes the hydrolysis of urea to ammonia and carbon dioxide.
   2. *Arginase* catalyzes the formation of urea and ornithine from arginine.
   3. *Guanase* catalyzes the hydrolysis of guanine to form xanthine and ammonia.
   4. *Adenase* catalyzes the hydrolysis of adenine to form hypoxanthine and ammonia.

E. *Carbonic anhydrase.* This enzyme catalyzes the formation of water and carbon dioxide gas from carbonic acid.

II. **Oxido-Reductases.** These are the enzymes that catalyze oxidation-reduction reactions.

A. *Dehydrogenases.* These enzymes catalyze the transfer of hydrogen atoms from a substrate (hydrogen donator) to another compound (the hydrogen acceptor).

B. *Oxidases.* These are enzymes that catalyze the union of molecular oxygen with a substrate.

C. *Peroxidases* catalyze oxidation-reduction reactions in which peroxides are the immediate oxidizing agents.

D. *Catalase* catalyzes the formation of water and molecular oxygen from hydrogen peroxide.

E. *Desmolases.* These are enzymes that catalyze the cleavage of the —C—C— linkage. In general, the reactions catalyzed by desmolases involve the oxidation of one portion of a molecule, with the simultaneous reduction of the other portion. Example: *Zymase* catalyzes the formation of ethyl alcohol and carbon dioxide from sugars.

Chemical Nature of Enzymes.—The enzymes that have been isolated in crystalline form have all been found to be proteins. As a general rule, the purified hydrolases have proved to be simple proteins, and the crystalline oxido-reductases have been conjugated proteins. Dehydrogenases appear to be simple proteins, but they are probably inactive except in the presence of suitable prosthetic groups (coenzymes) that combine with them in the tissues.

TABLE XIV

SOME ENZYMES THAT HAVE BEEN ISOLATED IN CRYSTALLINE FORM

CRYSTALLINE ENZYMES	SUBSTRATES	END PRODUCTS
Urease	Urea	Ammonia, carbon dioxide
Pepsin	Proteins	Proteoses, peptones
Trypsin	Proteins, proteoses, peptones	Peptides
Chymotrypsin	Proteins, proteoses, peptones	Peptides
Carboxypeptidase	Polypeptides	Peptides, amino acids
Catalase	Hydrogen peroxide	Water, oxygen

Some Factors Affecting the Rate of Enzyme-Catalyzed Reactions.—*Concentration of the enzyme.* It is believed by most biochemists that enzymes catalyze reactions by combining momentarily with the reacting compounds (or compound). After the reaction is completed, the enzyme is freed, and can catalyze the reaction of other molecules in its vicinity. This theory is supported by the finding that the rate of enzyme-catalyzed reactions is accelerated by increasing the concentration of the enzyme. That is to say, the reaction can proceed more rapidly if more enzyme molecules are present to act as catalysts.

Temperature. The rate of most chemical reactions is increased two or three times when the temperature is raised 10° C. This is true also for enzyme-catalyzed reactions, provided the temperature is not raised above a certain critical value. Above this critical value, the enzyme becomes inactivated. This is evidence that enzymes are proteins, since proteins become denatured at elevated temperatures. The temperature at which an enzyme is most effective is called the *optimum temperature.* Most of the enzymes of warm-blooded animals have optimum temperatures in the neighborhood of 40° C.

pH. For every enzyme there is a pH value at which the enzyme is most active. For example, wheat-flour amylase is most effective at pH 4.8; if the pH is lowered below 2, or is raised above 9, the enzyme is almost entirely inactive. The optimum pH for a given enzyme varies somewhat, depending on the substrate, the salts present in the test solution, and the source of the enzyme. For example, the optimum pH for pepsin is 1.8 when casein is the substrate, but is 2.2 if hemoglobin is substituted for casein. Salivary amylase has an optimum pH of 5.6 in acetate solutions, and of 6.5 in phosphate solutions. The lactase present in yeast has an optimum pH of 7.0; almond lactase is most effective at pH 4.2.

Miscellaneous factors. Any substance or procedure that causes denaturation of proteins also will inactivate enzymes. Thus, enzyme activity is inhibited or prevented by salts of heavy metals, organic protein precipitants (sulfosalicylic acid, tannic acid, trichloroacetic acid, etc.), and ultraviolet radiant energy.

Enzyme Specificity.—Enzymes are said to be *specific.* This means that given enzymes will catalyze the hydrolysis or oxidation-reduction of only certain *types* of chemical linkages or groups. For example, proteinases will catalyze the hydrolysis of proteins, but not of lipids. Catalase, which catalyzes the conversion of hydrogen peroxide to water and oxygen, will not catalyze the hydrolysis of proteins.

Proenzymes.—Proenzymes are substances that become active enzymes in the presence of a suitable activating substance. The lining of the stomach secretes a protein known as pepsinogen; in the presence of the hydrochloric acid in gastric (stomach) juice, pepsinogen becomes the active enzyme, pepsin. The pancreatic enzyme, trypsin, is formed when its proenzyme, trypsinogen, comes in contact with enterokinase, a substance present in the small intestine. Substances that convert proenzymes to active enzymes frequently are known as *kinases.*

Activators and Inhibitors.—Certain ions or organic compounds affect enzyme activity. In some cases, the effect is to accelerate the enzyme activity; in other cases, the effect is a slowing of the enzyme-catalyzed reaction. Some examples of enzyme activators and inhibitors follow:

Activators: Magnesium ions activate bone phosphatase; cobalt and manganese ions activate arginase; chloride ions activate amylase; cyanide ions activate papain (a proteinase); hydrogen sulfide and cysteine activate urease.

Inhibitors: Heavy metal ions, reagents that combine with protein amino groups (nitrous acid, ketene, etc.), oxidizing agents, and the anti-enzymes (protein substances that inactivate specific enzymes) found in animal tissues are examples of inhibitors. Hydrogen cyanide activates some enzymes (papain, cathepsin, urease), but it inactivates certain essential oxidation-reduction catalysts of the body. Due to this inactivation, hydrogen cyanide is a deadly poison.

Coenzymes.—Certain organic substances present in tissues are known as *coenzymes.* Coenzymes combine with specific proteins to form active enzyme systems. In most cases, the protein is what we have termed a dehydrogenase. However, in spite of this classification of the protein as an enzyme, it must be emphasized that *it is inactive in the absence of the appropriate coenzyme.*

Coenzymes act as hydrogen acceptors. In the presence of the necessary protein (dehydrogenase), hydrogen atoms are transferred from substrate (hydrogen donator) molecules to coenzyme molecules. Other substances present in tissues then remove the hydrogen atoms from the coenzyme, which then takes more hydrogen atoms from the original substrate. This process can continue until the substrate is oxidized completely. A more detailed example of coenzyme activity will be given in Chapter XXIII.

Several members of the vitamin B complex are known to be present in certain coenzymes that take part in the normal chemical reactions of living, healthy tissues.

Autolysis.—*Cathepsin* is the name given to a mixture of proteinases present in all, or nearly all, cells. These enzymes, like urease and the plant proteinase, papain, are activated by cyanide ions, hydrogen sulfide, and cysteine. Probably cathepsin is inactive in healthy tissue, since its optimum pH is in the neighborhood of 4. (The pH of the interior of a cell probably is about 6.8; the pH of blood is about 7.4.) After death, acid substances (such as lactic acid, sulfuric acid, and phosphoric acid) accumulate in the cells, and the intracellular pH falls. This causes cathepsin to become active, and the dead cells liquefy as a result of the hydrolysis of their proteins. This liquefaction of tissues after death is called *autolysis.* Much of the disintegration of dead tissue is caused by bacterial enzymes, but autolysis occurs even when bacteria are not present. Partial autolysis is responsible for the increased tenderness of meat that has been aged at a low temperature.

Study Questions

1. Define: enzyme, substrate, end product.
2. What is a reversible reaction? How is a reversible reaction affected by the presence of a suitable enzyme?
3. Do enzymes change the equilibrium points of reversible reactions?
4. Explain how an enzyme that catalyzes the breakdown of a substrate also can catalyze its synthesis.
5. What is the modern method of naming enzymes? Why do the names of many enzymes end in *in?*
6. In general, what two types of chemical reaction are catalyzed by enzymes?
7. Make a list of the more important types of enzymes, and give a definition of each.
8. What type of chemical compound are enzymes thought to be? List several reasons for this belief.
9. Name several enzymes that have been isolated in crystalline form. Give the substrate and end products for each.

10. How is the rate of an enzyme-catalyzed reaction altered if the concentration of the enzyme is increased? Explain.
11. What is mean by the optimum temperature of an enzyme? Why are enzymes inactivated if the temperature is raised too high?
12. At which one of the following temperatures would pepsin (an enzyme found in the stomach) be most active: 0° C., 40° C., 100° C.? Explain.
13. What is meant by the optimum pH of an enzyme? List some factors that alter the optimum pH.
14. List two or three other factors that influence the rate of enzyme-catalyzed reactions.
15. What is meant by enzyme specificity?
16. What are proenzymes? Kinases?
17. Define: enzyme activator; enzyme inhibitor. Give some examples of each.
18. Why is hydrogen cyanide poisonous? Why is a mixture of potassium cyanide and sulfuric acid often used in fumigating houses?
19. Give a definition of coenzyme. Are coenzymes inactivated by boiling their solutions? Explain.
20. Is a dehydrogenase active in the absence of coenzymes? Do you think the term *dehydrogenase* should be abandoned, and the term *activator protein* used instead, as some scientists have suggested? Explain.
21. What three vitamins are known to be present in various natural coenzymes?
22. What is cathepsin? What substances can be used to activate it?
23. What is autolysis? Why does it not occur in healthy, living tissue?
24. Explain why meat becomes more tender if it is aged at low temperatures. Why must the temperature be low?

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CHAPTER XXIII

THE CHEMISTRY OF RESPIRATION

Introduction.—*Metabolism* may be defined as the sum total of all the chemical reactions that take place in living tissues. Some of these reactions result in the synthesis of larger molecules from smaller ones. In most cases these larger molecules are used in building new tissue, or are stored, later to be broken down with the release of energy. All of us know, for example, that, if we eat more than we need, much of the excess food is converted to fat. In time of need this stored fat can be burned (oxidized) with the production of water, carbon dioxide, and energy. The phase of metabolism that results in the storage of new molecules and chemical energy in the tissues is called *anabolism.* Reactions that result in the formation of smaller molecules from larger ones with the release of energy are called *catabolic* reactions.

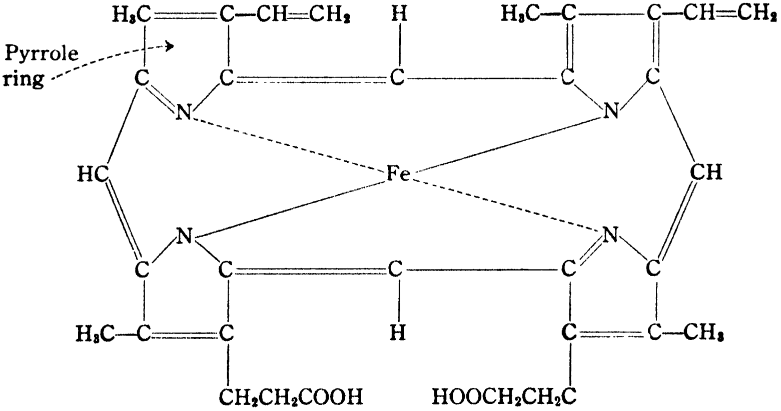
To the chemist, *respiration* is that phase of catabolism in which the tissues utilize oxygen and produce carbon dioxide. Essentially, the story of respiration is the story of the transport of oxygen from the lungs to the tissues; of its union there with the hydrogen that is removed from food molecules by respiratory (oxidation-reduction) enzymes; and of the eventual elimination of carbon dioxide and water from the body.

The Transport of Oxygen to the Tissues

In the short space of a minute, each of us, under average conditions, absorbs about 350 cc. of oxygen and eliminates about 315 cc. of carbon dioxide. Less than 2 per cent of this oxygen is carried from the lungs to the tissues in simple solution in the blood. The remainder diffuses from the air in the lungs into the red blood cells. In these cells it combines with the red protein, hemoglobin. In the tissues, hemoglobin releases a part of its oxygen and returns to the lungs for a fresh supply.

Hemoglobin.—Hemoglobin is the red pigment of the blood. Normally, all of it is contained within the red blood cells; that is, none of it is present in the plasma, or liquid portion of the blood. About 96 per cent of the molecule is composed of a histone, called *globin.* The other 4 per cent is an iron-containing substance called *heme.*

Heme belongs to the class of organic substances known as the porphyrins. Its molecule is composed of 4 pyrrole rings linked to each other by carbon atoms. Two of these rings also are linked by means of an iron atom.



Formula postulated for heme

(The dotted lines indicate that some of the electrons in the outer shells of the nitrogen atoms have a weak affinity for the iron.)

It has been found that one gram-atomic weight of iron is present in about 16,500 g. of hemoglobin. Actual measurements of the molecular weight of hemoglobin give a value of approximately 68,000. Thus it appears that a molecule of hemoglobin contains 4 molecules of heme. Each of the iron atoms of the heme can combine with one molecule (2 atoms) of oxygen. This union is a very loose one, however, and is not the result of a true oxidation-reduction reaction; that is, the valence of the iron of oxyhemoglobin (hemoglobin combined loosely with oxygen) is the same (2+) as that of the iron present in reduced hemoglobin, which does not contain loosely bound oxygen.

Some Substances Related to Hemoglobin.—*Methemoglobin.* When fresh meat is cooked, its color changes from red to brown. This color change is due to the conversion of hemoglobin to *methemoglobin.* The iron of methemoglobin has a valence of 3, and is no longer capable of uniting loosely with oxygen. The prosthetic (nonprotein) group of methemoglobin often is called *hematin.* Its formula probably is like that of heme, except that an OH group is attached to the iron.

Acid hematin. Treatment of hemoglobin, or of blood, with 0.1 N hydrochloric acid results in the formation of a brown pigment known as *acid hematin.* Acid hematin probably is a conjugated protein in which the prosthetic group is identical with hematin, except that the OH group of the latter is replaced by a Cl atom. The dilution of blood with dilute hydrochloric acid and comparison of the color of the acid hematin solution thus formed with a suitable standard is the basis of a widely used method for the analytical determination of hemoglobin.

Hemin. When blood is treated with glacial acetic acid and sodium chloride, microscopic crystals of *hemin* form. These crystals have a brown color and a characteristic rhomboid shape. Hemin has been synthesized. Its structure is like that shown for heme, except that a chlorine atom is attached to the iron. Hemin, like other heme derivatives in which the iron has a valence of 3, will not combine loosely with molecular oxygen.

The formation of hemin crystals can be used as a chemical test for the presence of blood.

Carbon monoxide hemoglobin. Carbon monoxide, like oxygen, will combine with the iron of reduced hemoglobin. As is the case with oxygen, this reaction is reversible. However, the affinity of hemoglobin for carbon monoxide is about 200 times as great as its affinity for oxygen. Stated differently, this means that one-half of the hemoglobin exposed to a mixture of 200 volumes of oxygen and one volume of carbon monoxide will be carbon monoxide hemoglobin. The other one-half will be oxyhemoglobin. Carbon monoxide is a poison, because the carbon monoxide hemoglobin formed from it cannot transport oxygen. Automobile exhaust gas and illuminating gas, both of which contain carbon monoxide, frequently are responsible for accidental deaths.

Transport of Oxygen by Hemoglobin.—One gram of hemoglobin is capable of combining loosely with 1.34 cc. of oxygen. The tension or partial pressure of the oxygen in the alveoli (air sacs) of the lungs is relatively high—about 100 mm. of mercury. As blood passes through the lungs, this pressure causes oxygen to diffuse into it and to combine with hemoglobin. Although a molecule of hemoglobin is in contact with alveolar oxygen only a very short time (all the blood in the body—about 5 to 7 liters—passes through the lungs once a minute), the hemoglobin in the blood leaving the lungs is 95 per cent saturated with oxygen. One hundred cubic centimeters of this oxygenated blood, which contains about 15 g. of hemoglobin, thus contains approximately 20 cc. of oxygen. In the tissues the oxygen tension is only 30 to 40 mm. of mercury, and some of the oxyhemoglobin changes to reduced hemoglobin. The venous blood returning to the lungs after its passage through the tissues contains in the neighborhood of 13 or 14 cc. of oxygen in each 100 cc.

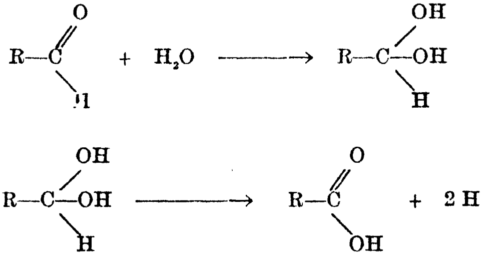
As we have just found, the low oxygen tension of the tissues favors the dissociation of oxyhemoglobin. Two other factors also favor this dissociation:

(1) The conversion of oxyhemoglobin to reduced hemoglobin is accelerated and made more complete by carbon dioxide. The relatively high carbon dioxide tension of the tissues increases the loss of oxygen from the blood.

(2) The amount of oxygen with which hemoglobin can combine at low oxygen tensions is reduced if the pH of the blood is lowered. Now, the pH of the blood changes from something like 7.43 (arterial blood) to about 7.25 (venous blood) as it circulates through the body. This change is due in part to the small quantities of carbonic acid (H_2CO_3) formed when carbon dioxide enters the blood, and partly to the diffusion from the tissues into the blood of organic acids (such as lactic acid) formed in metabolism.

The Transport of Hydrogen in the Tissues

Most of the oxidations in living organisms involve essentially *the removal of hydrogen from food molecules.* In some cases this removal of hydrogen is preceded by an addition of water. Since water contains both hydrogen and oxygen, the net result of both of these reactions will be a loss of hydrogen and an addition of oxygen to the food molecule. We may picture the biological oxidation of an aldehyde to an acid as follows:



$$R\text{—}C(=O)\text{—}H + H_2O \longrightarrow R\text{—}C(OH)(OH)\text{—}H$$

$$R\text{—}C(OH)(OH)\text{—}H \longrightarrow R\text{—}C(=O)\text{—}OH + 2\,H$$

The hydrogen atoms formed in this type of oxidation are transported by a sort of "bucket brigade" of substances in the tissues. Finally, they combine with oxygen to form either water or hydrogen peroxide (H_2O_2).

Hydrogen peroxide is a poison, since it causes denaturation and precipitation of proteins. Hydrogen peroxide accumulation is prevented by *catalase,* an enzyme present in all the tissues of the body. This substance catalyzes the conversion of hydrogen peroxide to water and molecular oxygen. Catalase contains iron, and its molecule is related chemically to that of hemoglobin.

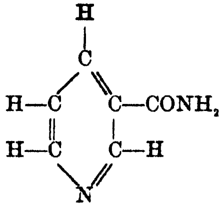
Dehydrogenases.—Enzymes that catalyze the transfer of hydrogen atoms from one substance to another are called *dehydrogenases.* The substance from which the hydrogen is removed is called the *hydrogen donator,* and the substance receiving the hydrogen is known as the *hydrogen acceptor.* Dehydrogenases, in common with other enzymes, are proteins. Probably they catalyze reactions by adsorbing both the hydrogen acceptor and the hydrogen donator. This brings the two reacting molecules close together and facilitates the transfer of hydrogen. After the hydrogen exchange is completed, the oxidized hydrogen donator and the reduced hydrogen acceptor are thought to leave the surface of the dehydrogenase, which then adsorbs a second pair of reacting molecules. This process continues until all of the hydrogen donator is oxidized.

In certain cases, oxygen can act as the hydrogen acceptor. Dehydrogenases capable of catalyzing reactions in which oxygen is involved are called *aerobic dehydrogenases.* In other cases, oxygen cannot act as the hydrogen acceptor; here, the enzyme is said to be an *anaerobic dehydrogenase.*

Coenzymes I and II.—Two complex substances, known as *coenzyme I (codehydrase I, cozymase)* and *coenzyme II (codehydrase II),* are important hydrogen acceptors. These substances are nucleotides, and yield the following compounds on hydrolysis:

Coenzyme I	*Coenzyme II*
1 molecule of nicotinic acid amide	1 molecule of nicotinic acid amide
2 molecules of phosphoric acid	3 molecules of phosphoric acid
2 molecules of ribose	2 molecules of ribose
1 molecule of adenine	1 molecule of adenine

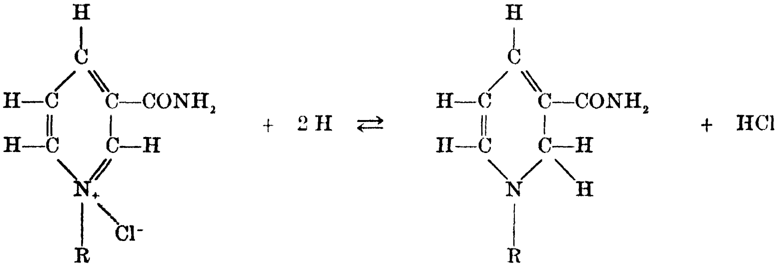
It has been suggested that coenzyme I, which contains two phosphoric acid groups in each molecule, be called diphosphopyridine nucleotide (D. P. N.), and that coenzyme II be called triphosphopyridine nucleotide (T. P. N.).



Nicotinic acid amide

The portion of the coenzyme molecule important in hydrogen transfer is the nicotinic acid amide, which is a pyridine derivative. In a later chapter (Chapter XXIX) we shall find that this substance is a vitamin and must be present in the diet.

When nicotinic acid amide is combined in the coenzyme molecule, the nitrogen is thought to be pentavalent. One of the two additional bonds is attached to the first carbon of a ribose molecule, and the other to some negative ion (for example, a chloride ion). The reversible reaction believed to occur when a coenzyme molecule accepts hydrogen atoms can be written as follows:



The first important respiratory reaction in the tissues is a transfer of hydrogen atoms from a food molecule to one of the coenzymes. This reaction is catalyzed by appropriate dehydrogenases. Sometimes this type of dehydrogenase is called a *zwischenferment* ("in between enzyme"). If we indicate the food molecule by FH_2 and the coenzyme molecule by Co, the reaction can be written schematically as follows:

$$FH_2 + Co \xrightarrow[\text{(Dehydrogenase)}]{} F + CoH_2$$

The partly oxidized food residue then reacts with a second molecule of coenzyme, and this process continues until oxidation is complete.

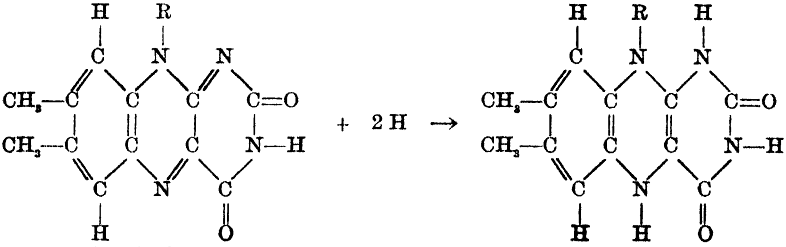
Flavoproteins.—As we have seen in the preceding discussion, coenzymes can take hydrogen from food substrates. The reduced coenzymes, in turn, transfer this hydrogen to other substances. The most important of these substances appear to be conjugated proteins. In the oxidized state these proteins have a yellow color; for this reason, they are called *flavoproteins* or *yellow enzymes.* Sometimes the terms *diaphorase* or *cytochrome reductase* are used for certain of them. (We shall find later that substances called cytochromes can be reduced by flavoproteins.)

The prosthetic groups of all the known flavoproteins yield flavin (alloxazine), ribose, and phosphoric acid on hydrolysis. In addition, certain flavoproteins contain combined adenine. These prosthetic groups, then, either are mononucleotides or dinucleotides. The hydrolytic products of the two types are listed below:

Mononucleotide type	*Dinucleotide type*
1 molecule of flavin (alloxazine)	1 molecule of flavin (alloxazine)
1 molecule of ribose	2 molecules of ribose
1 molecule of phosphoric acid	2 molecules of phosphoric acid
	1 molecule of adenine

Riboflavin, the nucleoside formed when phosphoric acid is removed from the mononucleotide type, is a member of the vitamin B complex (see Chapter XXIX). In common with other vitamins, it cannot be synthesized in the body, and is an essential ingredient of the diet.

In the presence of reduced coenzyme, the flavin molecule of the flavoprotein takes on two hydrogen atoms.



Oxidized form Reduced form

If we use the symbol FP to indicate flavoprotein, the reaction may be represented as follows:

$$CoH_2 + FP \rightarrow Co + FPH_2$$

The oxidized coenzyme formed by this reaction can be reduced again by the transfer of two more hydrogen atoms from a food molecule.

Cytochromes.—The next link in the chain of hydrogen acceptors is represented by the *cytochromes.* Cytochromes are conjugated proteins. Their prosthetic groups contain iron and are related chemically to heme. The iron of reduced cytochrome has a valence of 2; that of oxidized cytochrome is trivalent. Three different cytochromes (called cytochromes a, b, and c) are known.

Cytochromes, for which we shall use the shorthand symbol Cy, can remove hydrogen from reduced flavoproteins.

$$\text{Cy} + \text{FPH}_2 \rightarrow \text{CyH}_2 + \text{FP}$$

The regenerated flavoprotein then can take more hydrogen atoms from reduced coenzymes.

Cytochrome Oxidase.—*Cytochrome oxidase (Warburg's respiratory enzyme, "Atmungsferment," indophenol oxidase)* is an iron-containing substance that appears to be present in all tissues. No one yet has succeeded in isolating it. However, there are excellent reasons for supposing that it contains iron as an essential part of its molecule. This enzyme, which we shall designate by the symbol RE, causes the oxidation of reduced cytochrome.

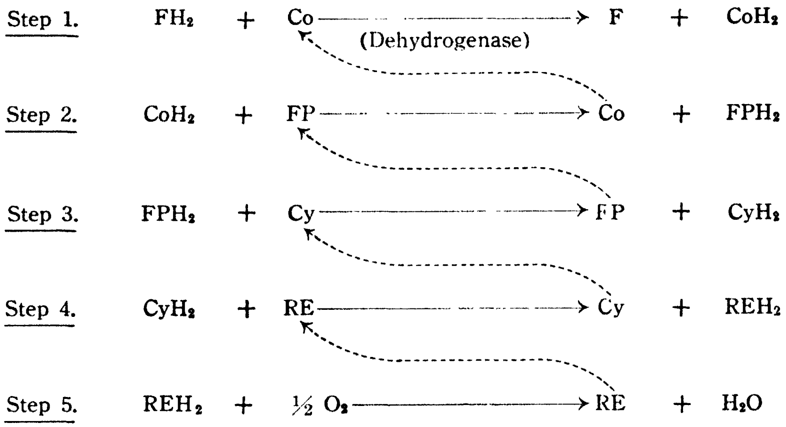
$$\text{CyH}_2 + \text{RE} \rightarrow \text{Cy} + \text{REH}_2$$

This reaction regenerates the cytochrome molecule, which can now receive more hydrogen from a reduced flavoprotein molecule. The cytochrome oxidase is returned to its active (oxidized) state by a reaction in which it transfers hydrogen to molecular oxygen.

$$\text{REH}_2 + \tfrac{1}{2}\,\text{O}_2 \rightarrow \text{RE} + \text{H}_2\text{O}$$

This step, in which water is formed, is the last of the reactions by means of which hydrogen is transported from a food molecule to molecular oxygen.

Summary.—*We can summarize the transport of hydrogen atoms from a food molecule to oxygen by means of the following symbolic equations:



Step 1. $FH_2 + Co \xrightarrow{} F + CoH_2$ (Dehydrogenase)

Step 2. $CoH_2 + FP \xrightarrow{} Co + FPH_2$

Step 3. $FPH_2 + Cy \xrightarrow{} FP + CyH_2$

Step 4. $CyH_2 + RE \xrightarrow{} Cy + REH_2$

Step 5. $REH_2 + \frac{1}{2} O_2 \xrightarrow{} RE + H_2O$

Most of the water formed by these reactions is eliminated from the body in the urine, in the sweat, and in the expired air. Small amounts are excreted in the feces, nasal secretions, tears, etc.

The Transport of Carbon Dioxide to the Lungs

Most of the potassium of the blood is inside the red blood cells; most of the blood sodium is in the plasma. With the exception of hydrogen ions, cations (positive ions) do not readily pass across the red blood cell membrane. With these facts in mind, we shall proceed to a discussion of the transport of carbon dioxide from the tissues to the lungs, where it is eliminated from the body.

At the pH of the blood, oxyhemoglobin is negatively charged. A part of this negative charge is neutralized by potassium ions. We shall represent the oxyhemoglobin (more correctly, potassium oxyhemoglobinate) molecule by means of the symbol $KHbO_2$.

As we have learned, tissue oxidations usually involve additions of water and removal of hydrogen. Eventually, sufficient oxygen is gained to enable the carbon atoms of the food molecules to split off as carbon dioxide. The tension of the carbon dioxide of the tissues amounts to about 47 to 50 mm. of mercury. At this tension the gas rapidly diffuses into the blood.

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*Numerous systems concerned with hydrogen transport occur in tissues. However, the existing evidence makes it likely that these systems include some or all of the substances mentioned in this summary as necessary components.

Transport of Carbon Dioxide by the Blood.—Now, when arterial blood reaches the capillaries, oxygen splits off, leaving, for a short time, reduced potassium hemoglobinate.

$$KHbO_2 \rightarrow KHb + O_2$$

Some of the carbon dioxide entering the blood diffuses through the red blood cell membrane. Inside the red cell there is a rapid formation of carbonic acid. This reaction is catalyzed by an enzyme called *carbonic anhydrase.*

$$CO_2 + H_2O \rightarrow H_2CO_3$$

Carbonic acid then reacts with potassium hemoglobinate, forming reduced hemoglobin, potassium ions, and bicarbonate ions.

$$KHb + H_2CO_3 \rightarrow HHb + K^+ + HCO_3^-$$

As the concentration of bicarbonate ions in the red blood cell increases, there is a marked tendency for these ions to diffuse across the membrane into the plasma. If we recall that potassium ions are unable to pass from the interior of the cell to the plasma, it becomes apparent that bicarbonate ions cannot pass across the membrane *unless some anion (negative ion) in the plasma simultaneously passes into the cell;* that is, positively charged ions cannot move very far away from negatively charged ones because of the attraction of the opposite electrical charges. The most abundant anion in the plasma is the chloride ion. Therefore, as bicarbonate ions enter the plasma from the red blood cells, anions (chiefly chloride ions) simultaneously pass into the cell. We may represent the situations before and after diffusion by the following simplified scheme:

Types of Ions Inside the Red Blood Cell	Types of Ions in the Plasma
Before Diffusion	*Before Diffusion*
K^+ and HCO_3^-	Na^+ and Cl^-
After Diffusion	*After Diffusion*
K^+, HCO_3^-, and Cl^-	Na^+, Cl^-, and HCO_3^-

Notice that not all the bicarbonate ions formed in the cell pass across the membrane. At equilibrium, about 60 per cent of the bicarbonate ions will be in the plasma; the other 40 per cent will be in the red blood cells. This passage of chloride ions into the red blood cells when carbon dioxide enters the blood is called the *chloride shift.*

A small amount of the carbon dioxide entering the red blood cells combines directly with the free amino (NH_2) groups of the hemoglobin to form carbamate linkages.

$$HHbNH_2 + CO_2 \rightarrow HHbNHCOOH$$

In summary, we may say that the carbon dioxide entering the blood from the tissues is transported to the lungs in the following forms:

(1) A small amount (about 5 per cent of the total) is transported in simple solution in the plasma.

(2) Another small amount (probably about 10 per cent) is transported by means of carbamate linkages.

(3) The majority is transported as bicarbonate. About 40 per cent of the bicarbonate ions is in the red blood cells, and about 60 per cent is in the plasma.

Passage of Carbon Dioxide From the Blood Into the Lungs.— When blood enters the blood vessels (capillaries) of the lungs, most of the reduced hemoglobin is converted to oxyhemoglobin.

$$HHb + O_2 \rightarrow HHbO_2$$

$HHbO_2$ is a stronger acid than HHb. In other words, it has a greater affinity for (tendency to form salts with) potassium ions than has HHb. The reactions that took place in the tissues, therefore, are reversed, with the rapid formation of $KHbO_2$ and H_2CO_3 in the red blood cells. In the presence of carbonic anhydrase, this H_2CO_3 quickly forms CO_2 and H_2O. The carbon dioxide tension of the alveoli (air sacs) of the lungs is about 40 mm. of mercury. This is less than that of the blood, and the carbon dioxide formed in the red blood cells diffuses first into the plasma, and then into the lungs. As the bicarbonate ions of the red blood cells disappear, bicarbonate ions and chloride ions pass across the cell membrane—bicarbonate ions into the cells, and chloride ions into the plasma. These reactions are rapid enough so that about 10 to 15 per cent of the free and combined carbon dioxide is removed during the passage of blood through the lung capillaries.

Potassium oxyhemoglobinate ($KHbO_2$), in contrast to reduced hemoglobin (HHb), has little tendency to form carbamates, and much of the carbamate carbon dioxide splits off as free gas. This free gas escapes into the lungs.

We can summarize the events taking place in the lungs by saying they are the reverse of the reactions taking place in the tissues. In the tissues, carbon dioxide enters the blood, where most of it is converted to bicarbonate. In the lungs, a portion of the bicarbonate (as well as a majority of the carbamate carbon dioxide) is converted to carbon dioxide gas, which escapes into the alveoli of the lungs.

Study Questions

1. Define: metabolism, anabolism, catabolism.
2. Give a chemical definition of respiration.
3. What substance is responsible for most of the color of the blood?
4. What type of organic compound is heme?
5. What is the valence of the iron combined in the heme molecule? Does this valence change when reduced hemoglobin is converted to oxyhemoglobin?
6. What type of protein is globin?
7. What is the approximate molecular weight of hemoglobin?
8. How many atoms of iron are believed to be present in one molecule of hemoglobin?
9. How many oxygen molecules can combine loosely with the iron present in a molecule of hemoglobin?
10. How does the prosthetic group of methemoglobin differ from that of reduced hemoglobin?
11. What is hematin?
12. How can acid hematin be formed? Will this substance combine loosely with molecular oxygen?
13. How can crystalline hemin be prepared? What is the valence of the iron in hemin? What halogen atom is present in its molecule?
14. Explain why carbon monoxide is a poison. What treatment do you suppose might be most effective for carbon monoxide poisoning? Explain.

15. How much loosely combined oxygen is present in 1 g. of fully oxygenated hemoglobin (oxyhemoglobin)?
16. What force causes oxygen to move from the alveoli of the lungs into the blood?
17. About how much blood passes through the lungs in an hour?
18. Calculate the approximate amount of hemoglobin present in the body.
19. How much loosely bound oxygen is present in 100 cc. of arterial blood?
20. What is the oxygen tension of the tissues?
21. List the factors that favor the conversion of oxyhemoglobin to reduced hemoglobin in the tissues.
22. What two chemical changes usually are involved in the oxidation of a food molecule in the body?
23. What enzyme prevents the accumulation of hydrogen peroxide in the tissues? Why is hydrogen peroxide a poison?
24. Define: dehydrogenase, hydrogen donator, hydrogen acceptor.
25. What is the postulated mechanism by which dehydrogenases catalyze the transfer of hydrogen atoms?
26. How do aerobic and anaerobic dehydrogenases differ?
27. What type of chemical compound is coenzyme I? Coenzyme II?
28. Give three synonyms for coenzyme I and two synonyms for coenzyme II.
29. List the products of hydrolysis of coenzymes I and II.
30. What portion of the coenzyme molecule is important in hydrogen transfer?
31. What vitamin is necessary for the formation of coenzymes I and II in the animal body?
32. Write an equation illustrating the transfer of hydrogen from a food molecule to a coenzyme molecule. What special name sometimes is given to the dehydrogenase catalyzing this reaction?
33. Give three synonyms for flavoprotein.
34. What type of protein is a flavoprotein?
35. List the products of hydrolysis of the two types of flavoprotein prosthetic group. Which of these products are present in the vitamin riboflavin?
36. Write an equation illustrating the transfer of hydrogen atoms from reduced coenzyme to flavoprotein.
37. What metal is present in the prosthetic groups of the cytochromes? What is its valence?
38. How many different cytochromes are known?
39. How many hydrogen atoms are required to reduce a molecule of cytochrome?
40. Give three synonyms for cytochrome oxidase.
41. What is believed to be the function of cytochrome oxidase?
42. What substance takes hydrogen from cytochrome oxidase?
43. What metal probably is present in the cytochrome oxidase molecule?

44. Write five equations summarizing the transfer of two hydrogen atoms from a food molecule to molecular oxygen.
45. What is the fate of the water formed in the tissues?
46. Are most of the potassium ions of the blood in the red blood cells or in the plasma? Most of the sodium ions?
47. Write a series of symbolic equations summarizing the chemical changes that take place when carbon dioxide enters the blood.
48. Write a series of symbolic equations summarizing the chemical changes that take place when carbon dioxide leaves the blood.
49. How do you explain the fact that carbonic anhydrase catalyzes the *formation* of carbonic acid in the tissues and the *breakdown* of carbonic acid in the lung capillaries?
50. What is meant by the term *chloride shift?* Explain why it occurs.
51. About what percentage of the combined carbon dioxide of the blood is transported as carbamate? As free gas?
52. What is the partial pressure (tension) of carbon dioxide in the tissues? In the alveoli of the lungs?
53. What percentage of the bicarbonate of the blood is in the plasma?
54. Which is the stronger acid, reduced hemoglobin or oxyhemoglobin?
55. Approximately what percentage of the free and combined carbon dioxide is removed during the passage of blood through the lungs?
56. Approximately what percentage of the loosely bound oxygen is removed during the passage of blood through the tissues?

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CHAPTER XXIV

CARBOHYDRATE METABOLISM

Digestion and Absorption

Digestion is the term used to designate a series of chemical reactions that take place in the digestive, or alimentary, tract. These reactions bring about the hydrolysis of certain substances present in food. Thus, the end products of digestion are all hydrolytic products. Carbohydrate digestion results in the formation of the three monosaccharides, glucose, fructose, and galactose, from certain polysaccharides (starch, dextrins, glycogen) and disaccharides (sucrose, maltose, lactose) present in the diet.

Salivary Digestion.—Saliva, the digestive fluid of the mouth, is more than 99 per cent water. Other substances present in it are mucin (a glycoprotein), inorganic salts, urea, and enzymes. Saliva moistens the mouth cavity and lubricates the food so that it can be swallowed easily. The lubricating power of saliva is due to the presence of mucin.

Salivary amylase catalyzes the conversion of starch to dextrins, and, finally, to maltose. Glycogen also yields maltose in its presence.

$$\text{Starch} \xrightarrow{+\ H_2O} \text{Dextrins} \xrightarrow{+\ H_2O} \text{Maltose}$$

$$\text{Glycogen} \xrightarrow{+\ H_2O} \text{Maltose}$$

Salivary maltase catalyzes the formation of glucose from maltose.

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow 2\,C_6H_{12}O_6$$

The mixture of amylase and maltase present in saliva frequently is called *ptyalin.*

Salivary amylase and maltase are extremely efficient at the pH of saliva (6.6 to 7.2). However, salivary digestion seldom is complete, because the food remains in the mouth only a short time. The salivary enzymes are not effective in the stomach, due to the fact that the gastric (stomach) juice contains free hydrochloric acid and has a pH much lower than that of the mouth. Digestion in the mouth is of importance chiefly because it causes the solution of food particles lodged between the teeth.

No enzymes important in the digestion of carbohydrates are present in gastric juice.

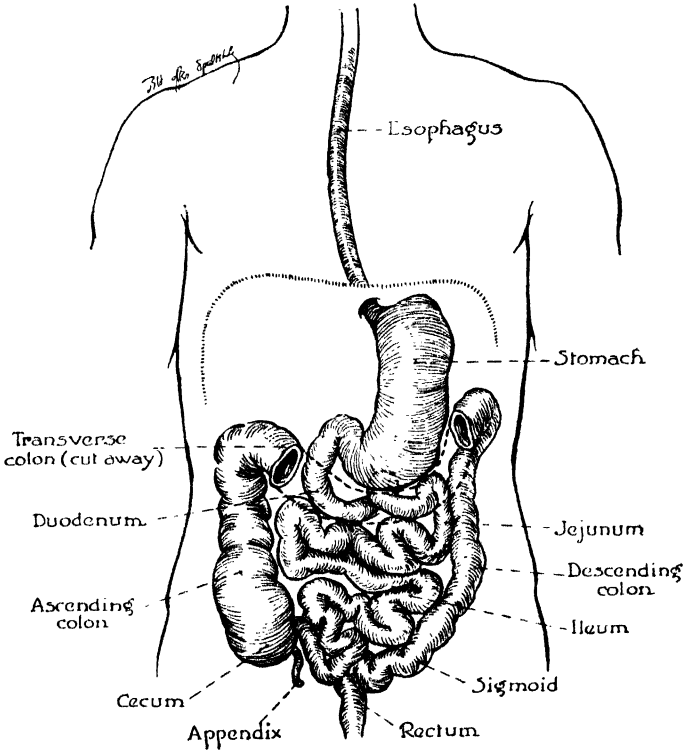


Fig. 64.—The digestive tract. Why must foods be digested? (From McClendon and Pettibone: Physiological Chemistry, The C. V. Mosby Co.)

Pancreatic Digestion.—The pancreas is a large gland that empties its digestive fluid (pancreatic juice) into the duodenum, or first part of the small intestine. Pancreatic juice is slightly alkaline, since it contains appreciable amounts of sodium bicarbonate. When this alkaline fluid enters the small intestine, it mixes with the acid juice coming from the stomach. As a result, the material in the small intestine usually is slightly acid (about pH 6.8). Pancreatic juice contains a number of important enzymes, four of which are concerned with carbohydrate digestion.

Pancreatic amylase (amylopsin) catalyzes the hydrolysis of starch and glycogen, with the formation of maltose. Any dex-

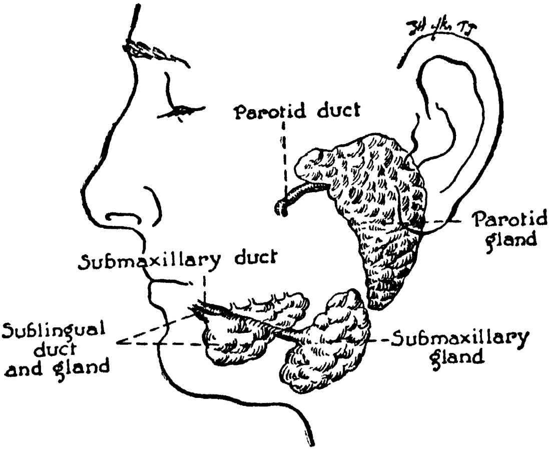


Fig. 65.—The salivary glands. What is the function of saliva? (From McClendon and Pettibone: Physiological Chemistry.)

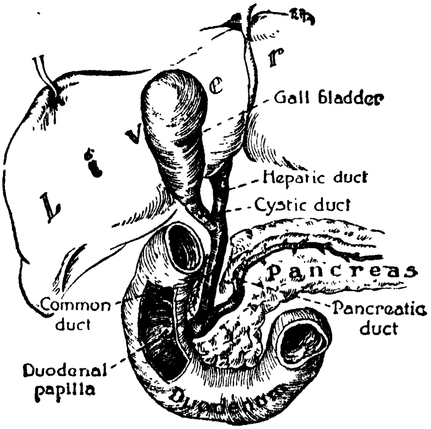


Fig. 66.—Drawing of the duodenum, pancreas, and liver. What pancreatic enzymes are concerned with carbohydrate digestion? (From McClendon and Pettibone: Physiological Chemistry.)

trins present also are converted to maltose. *Pancreatic maltase, sucrase (invertase, saccharase), and lactase* catalyze the hydrolysis of the disaccharides, maltose, sucrose, and lactose.

1 maltose + H_2O $\longrightarrow$ 2 glucose
1 sucrose + H_2O $\longrightarrow$ 1 glucose + 1 fructose
1 lactose + H_2O $\longrightarrow$ 1 glucose + 1 galactose

Intestinal Digestion.—The mucous membrane lining the small intestine secretes a fluid called *intestinal juice (succus entericus)*. This fluid contains sodium bicarbonate and is slightly alkaline. As we have learned already, ordinarily sufficient hydrochloric acid to neutralize this bicarbonate enters the intestine from the stomach. Intestinal juice contains a maltase, a sucrase, and a lactase.

Bacterial Action in the Intestine.—Many types of bacteria are present in the lower end of the small intestine and in the large intestine. Indeed, about one-fourth to one-half the dry weight of the stools is due to the presence of microorganisms. Certain of these bacteria decompose indigestible carbohydrates (celluloses, hemicelluloses, etc.), with the formation of methane, hydrogen, carbon dioxide, and organic acids. The organic acids thus formed are slightly irritant to the intestine, and it is probable that most of the laxative effect of so-called "bulk foods" (i.e., foods that contain a high percentage of indigestible carbohydrate) is to be traced to this irritant effect.

Absorption.—The final end products of carbohydrate digestion are glucose, fructose, and galactose. These substances pass from the intestinal tract into the blood, which then distributes them throughout the body.

In the presence of intestinal phosphatase, an enzyme present in the intestinal mucosa, glucose, fructose, and galactose can combine reversibly with phosphoric acid to form esters. Two possible explanations of the metabolic importance of this reaction have been offered:

(1) Perhaps this formation of phosphate esters is merely a reflection of the carbohydrate metabolism of the intestine. As we shall find later, hexose phosphates are formed when sugars are metabolized in the body.

(2) Perhaps the phosphate esters are concerned directly with the absorption of the monosaccharides from the digestive tract. This theory assumes that the monosaccharide phosphate formed as a result of the reaction rapidly leaves the interior of the intestine and passes into the intestinal mucous membrane. In the interior of this membrane the concentration of *free* monosaccharide is very low, and the phosphoric acid ester hydrolyzes, with the formation of free sugar and phosphoric acid:

$$\text{Monosaccharide phosphate} + H_2O \underset{\leftarrow}{\xrightarrow{\qquad}} \text{Monosaccharide} + \text{Phosphoric acid}$$

Most of the phosphoric acid released in this reaction (it is assumed) diffuses back into the intestine, where it unites with a second molecule of monosaccharide. The free monosaccharide (glucose, fructose, or galactose), after its formation in this way in the mucous membrane of the intestine, is assumed to pass directly into the blood.

Intermediary Metabolism

Intermediary metabolism is a term used to indicate the phases of metabolism that take place within the body tissues. In other words, this type of metabolism includes the chemical reactions that occur after the products of digestion have been absorbed, but before their waste products have been eliminated from the body.

Fate of Fructose and Galactose.—If fructose is injected into the blood stream of an animal, the amount of glycogen present in the animal's tissues increases. This indicates that fructose can be converted to glycogen in the animal body. When glycogen breakdown occurs, the only free monosaccharide formed is glucose. From these facts, we are led to conclude that most of the fructose absorbed from the intestinal tract eventually becomes glucose. Other experiments have demonstrated that animals from which the intestine and liver have been removed are unable to convert fructose to glucose. If either of these organs is present, the conversion occurs. These results show that the sites of the conversion of fructose to glucose are the liver and the intestine.

A small amount of fructose appears to be used by the tissues without a preliminary conversion to glucose. If fructose is injected into the blood of an animal from which the liver, kidneys, and intestine have been removed, and the entire carcass of the animal later is analyzed, it is found that some of the injected fructose has disappeared. Presumably, this fructose underwent some sort of chemical change in the tissues.

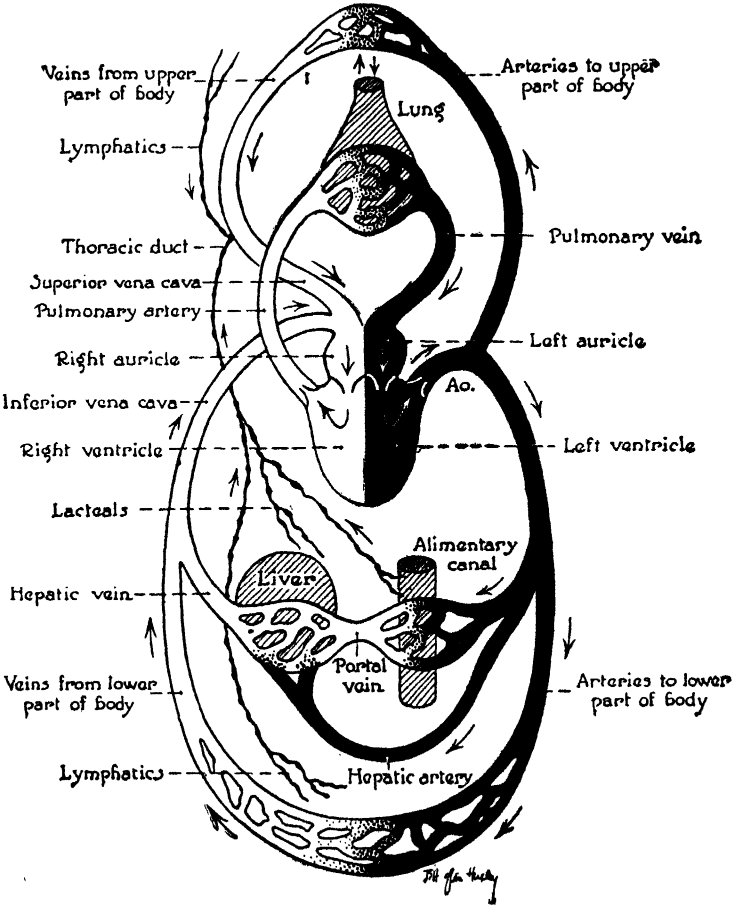


Fig. 67.—Diagram of blood circulation. Notice that blood leaves the digestive (alimentary) tract through the portal vein. What is the first organ reached by a glucose molecule after it leaves the digestive tract? (From McClendon and Pettibone: Physiological Chemistry, The C. V. Mosby Co.)

Experiments similar to those cited have shown that galactose is converted to glucose in the body. This conversion occurs in the liver, but not in the intestine. Probably very small amounts of galactose can be used as such by the tissues.

It is apparent that the intermediary metabolism of fructose and galactose is largely the intermediary metabolism of glucose, since these substances are converted chiefly to glucose in the body.

Glycogen Formation.—Glycogenesis (glycogen formation) occurs chiefly in the liver and in the muscles. The blood leaving the intestine passes into the portal vein, through which it flows directly to the liver. The excess glucose in this blood is removed by the liver and converted to glycogen. Many other substances (fructose, galactose, lactic acid, glycerol, some amino acids, fatty acids with an odd number of carbon atoms in each molecule, and so on) also can be converted to glycogen by the liver.

Blood leaving the liver is distributed to all the other regions of the body. As it passes through the muscles, some of its glucose is removed and converted to muscle glycogen.

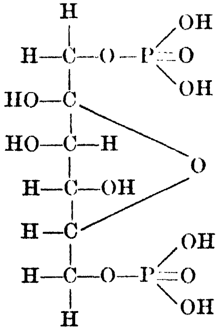
Glycogenolysis.—As the need for glucose arises, liver glycogen breaks down (undergoes glycogenolysis) to form it. When muscle glycogen breaks down, however, free glucose never is formed. Instead, muscle glycogenolysis results in the production of pyruvic and lactic acids. These acids either may be converted back to glycogen again, or they may be burned (oxidized), with the formation of carbon dioxide, water, and energy.

The Blood Sugar Level.—Practically all the sugar normally present in the blood is glucose. The average normal fasting level of blood sugar varies from about 70 to about 100 mg. per 100 cc. of blood. The organ that has most to do with the maintenance of the blood sugar at this level is the liver. When the level becomes too low, liver glycogen breaks down, and the glucose formed diffuses into the blood. If the level becomes too high, the liver removes the excess sugar and stores it as glycogen.

The kidneys also assist in preventing too large an increase in the blood sugar level. Normally, almost no sugar is present in the urine. However, when the blood level exceeds a critical value, called the *renal threshold,* sugar appears in the urine and is excreted. The average normal value of the renal threshold for sugar is about 150 to 170 mg. per 100 cc. of blood.

Chemical Changes in Muscle Contraction.—When a muscle contracts, a series of chemical reactions takes place within it. As a result of these reactions, muscle glycogen is converted to pyruvic and lactic acids. A portion (about one-fifth) of these acids is oxidized to carbon dioxide and water; the remainder is converted to glycogen again, either in the muscle or (after diffusion into the blood) in the liver. If large amounts of them are formed, some excretion in the urine may occur.

Anaerobic phase. The formation of pyruvic and lactic acids from muscle glycogen takes place under anaerobic conditions; that is, the reactions involved do not require oxygen. In the first known reaction, glycogen combines with inorganic phosphate and is converted to glucose-1-phosphate. This compound then rearranges to form, successively, glucose-6-phosphate and fructose-6-phosphate. Fructose-6-phosphate next combines with phosphoric acid to form fructose-1,6-diphosphate.



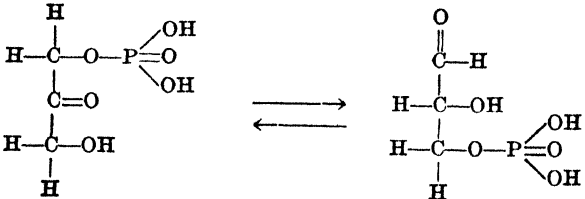
Fructose-1,6-diphosphate

The phosphoric acid required for this latter reaction comes from the breakdown of adenosine triphosphate (adenylpyrophosphate). A molecule of this substance is composed of a molecule of adenine combined with a molecule of ribose and three molecules of phosphoric acid. When it breaks down in metabolic reactions, one molecule of adenosine diphosphate and a molecule of phosphoric acid are formed. When adenosine diphosphate breaks down, a molecule of adenylic acid and a molecule of phosphoric acid are produced. These reactions are reversible. If we use the symbol ATP to represent adenosine triphosphate, ADP to mean adenosine diphosphate, P to indicate phosphoric acid, and AA to represent adenylic acid, the above reactions can be written symbolically as follows:

$$\begin{tikzcd} ATP \arrow[r, shift left] & ADP \arrow[l, shift left] \arrow[d, shift left] & + & P \\ & AA \arrow[u, shift left] & + & P \end{tikzcd}$$

The chemical bonds uniting the phosphoric acid radicals with adenylic acid to form ADP and ATP are referred to as "energy rich" phosphate bonds. This term is used because a considerable amount of energy is released when ATP is hydrolyzed to ADP and P, and when ADP is hydrolyzed to AA and P. In many cases, when oxidation occurs in metabolism, it is accompanied by the simultaneous production of "energy rich" phosphate bands. That is to say, the oxidation is accompanied by the simultaneous production of ATP or ADP from AA and phosphate. In this way, the energy released by the oxidation is stored in phosphate bonds. By means not yet understood, this phosphate bond chemical energy can be converted into the other types of energy (such as the mechanical energy of a contracting muscle) required by the body.

In the next step, the fructose diphosphate molecule breaks down to form two triose molecules.

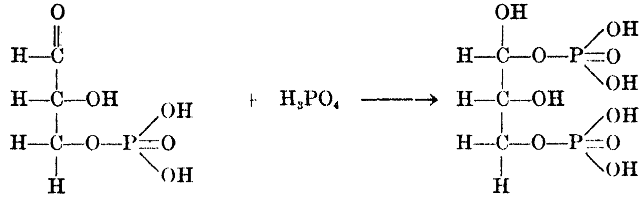


Dihydroxyacetone phosphate

Phosphoglyceric aldehyde

These two substances are in equilibrium with each other; that is, removal of either of them causes a rapid new synthesis of it at the expense of the other.

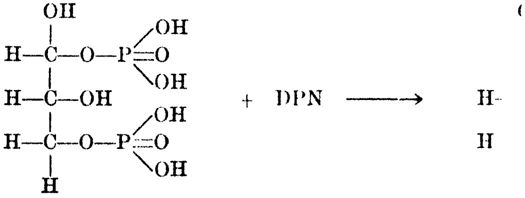
Phosphoglyceric aldehyde combines with inorganic phosphate to form diphosphoglyceric aldehyde.



Phosphoglyceric aldehyde

Diphosphoglyceric aldehy

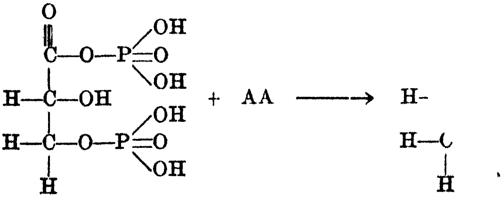
In the next step, diphosphoglyceric acid is
diphosphoglyceric aldehyde. Coenzyme I,
phosphopyridine nucleotide or DPN (see pag
for this reaction.



Diphosphoglyceric aldehyde

Di

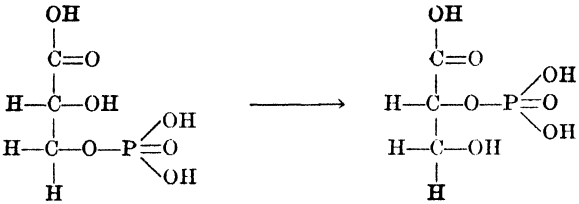
The diphosphoglyceric acid then lo
groups to adenylic acid (thus formin
phate bond) and becomes phosphogly



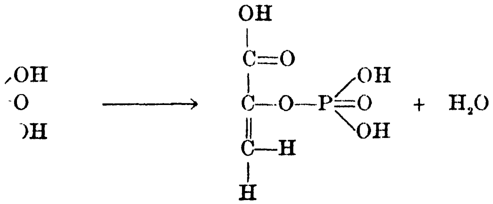
Diphosphoglyceric acid

Phosphoglyce acid

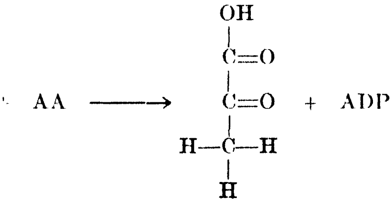
The β-phosphoglyceric acid formed in this reaction next rearranges to form α-phosphoglyceric acid.


β-Phosphoglyceric acid α-Phosphoglyceric acid

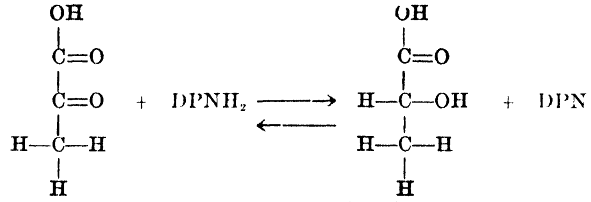
The enol form of phosphopyruvic acid is produced by the dehydration of the α-phosphoglyceric acid.


Phosphopyruvic acid (enol form)

d then loses its phosphate to adenylic
o free pyruvic acid.


Pyruvic acid

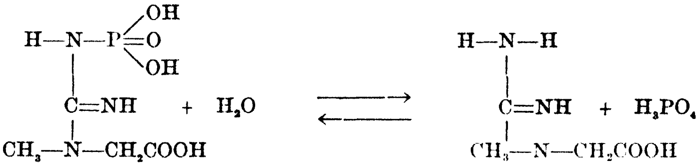
vic acid may take hydrogen from reduced
ic acid. As will be seen later, however, in
an adequate oxygen supply the oxidation of
es place by another mechanism.



$$\mathrm{HO{-}C({=}O){-}C({=}O){-}CH_3} + \mathrm{DPNH_2} \rightleftarrows \mathrm{HO{-}C({=}O){-}CH(OH){-}CH_3} + \mathrm{DPN}$$

Pyruvic acid Lactic acid

Muscle tissue contains a substance called creatine phosphate (phosphocreatine). During the anaerobic phase of muscle contraction, this substance breaks down reversibly to yield creatine and phosphoric acid.



$$\mathrm{H{-}N(P({=}O)(OH)_2){-}C({=}NH){-}N(CH_3){-}CH_2COOH} + \mathrm{H_2O} \rightleftarrows \mathrm{H{-}N(H){-}C({=}NH){-}N(CH_3){-}CH_2COOH} + \mathrm{H_3PO_4}$$

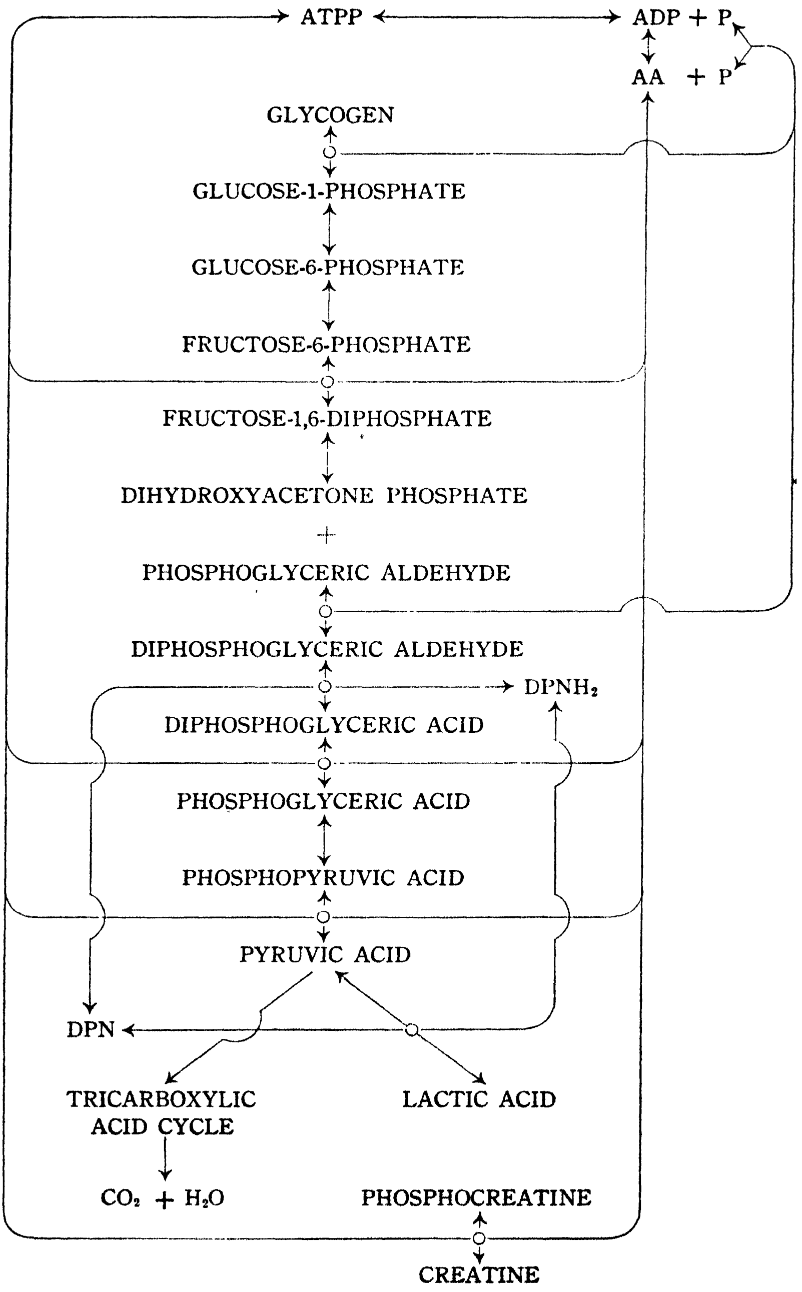
Creatine phosphate Creatine

Probably the phosphoric acid released by this hydrolysis is used in the resynthesis of adenosine triphosphate and adenosine diphosphate from adenylic acid.

The various phosphatases that catalyze the formation and hydrolysis of the phosphoric acid esters concerned in muscle glycogenolysis require *magnesium ions* for maximum efficiency.

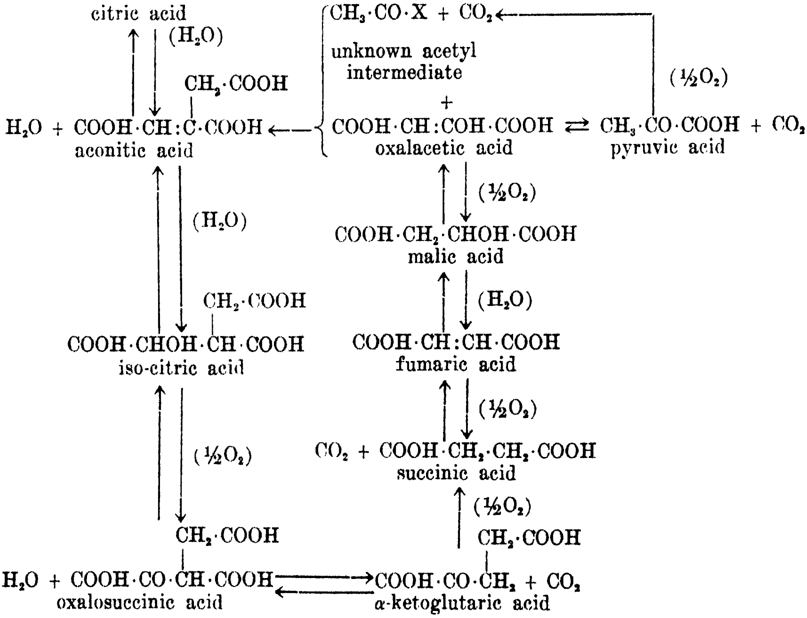
The outline on page 616 summarizes the important reactions that occur during the anaerobic phase of muscle glycogenolysis.

Aerobic phase. Since the reactions just described are anaerobic ones, it is apparent that a muscle can contract in the complete absence of oxygen. However, under these conditions the muscle soon fatigues. In other words, recovery of the muscle after it has contracted requires oxygen. This oxygen is used in the oxidation of approximately one-fifth of the pyruvic acid and lactic acid formed during the anaerobic phase. This oxidation results in the formation of carbon dioxide, water, and energy. The energy released by it is utilized in resynthesizing glycogen in order that the muscle again will be able


ATPP
ADP + P
AA + P
GLYCOGEN
GLUCOSE-1-PHOSPHATE
GLUCOSE-6-PHOSPHATE
FRUCTOSE-6-PHOSPHATE
FRUCTOSE-1,6-DIPHOSPHATE
DIHYDROXYACETONE PHOSPHATE
+
PHOSPHOGLYCERIC ALDEHYDE
DIPHOSPHOGLYCERIC ALDEHYDE
DPNH$_2$
DIPHOSPHOGLYCERIC ACID
PHOSPHOGLYCERIC ACID
PHOSPHOPYRUVIC ACID
PYRUVIC ACID
DPN
TRICARBOXYLIC ACID CYCLE
LACTIC ACID
CO$_2$ + H$_2$O
PHOSPHOCREATINE
CREATINE

to contract. After a muscle has contracted and recovered, the only apparent change is the loss of about one-fifth of the glycogen used during the contraction.

The evidence available at present makes it probable that the oxidation of pyruvic acid begins with its conversion in the tissue into a larger molecule, after which stepwise oxidation and decarboxylation yield carbon dioxide and water. Although the details of these chemical reactions are not known with certainty, most biochemists that are experts in the field of tissue respiration believe that the oxidation of pyruvic acid occurs mainly by way of the so-called *tricarboxylic acid cycle.* The various reactions believed to make up this cycle are given in the following series of reactions.


citric acid
(H_2O)
$CH_2{\cdot}COOH$
$H_2O + COOH{\cdot}CH{:}C{\cdot}COOH$
aconitic acid
$CH_3{\cdot}CO{\cdot}X + CO_2$
unknown acetyl intermediate
+
$COOH{\cdot}CH{:}COH{\cdot}COOH \rightleftarrows CH_3{\cdot}CO{\cdot}COOH + CO_2$
oxalacetic acid
pyruvic acid
($\frac{1}{2}O_2$)
($\frac{1}{2}O_2$)
$COOH{\cdot}CH_2{\cdot}CHOH{\cdot}COOH$
malic acid
(H_2O)
(H_2O)
$CH_2{\cdot}COOH$
$COOH{\cdot}CHOH{\cdot}CH{\cdot}COOH$
iso-citric acid
$COOH{\cdot}CH{:}CH{\cdot}COOH$
fumaric acid
($\frac{1}{2}O_2$)
($\frac{1}{2}O_2$)
$CO_2 + COOH{\cdot}CH_2{\cdot}CH_2{\cdot}COOH$
succinic acid
($\frac{1}{2}O_2$)
$CH_2{\cdot}COOH$
$CH_2{\cdot}COOH$
$H_2O + COOH{\cdot}CO{\cdot}CH{\cdot}COOH \rightleftarrows COOH{\cdot}CO{\cdot}CH_2 + CO_2$
oxalosuccinic acid
α-ketoglutaric acid

Several interesting points should be noted in studying this cycle of reactions. Until recently, it was believed that CO_2 was entirely a waste product of animal metabolism, although it was known, of course, that plants use this gas to synthesize carbohydrate (see page 512). Recent studies with carbon dioxide containing heavy carbon or radioactive carbon have made it evident that carbon dioxide can and does enter into metabolic reactions in animal tissues. For example, as shown in the tricarboxylic acid cycle, carbon dioxide can combine with pyruvic acid to form oxalacetic acid.

The most puzzling feature of the cycle is the identity of the two-carbon compound (labeled "unknown acetyl intermediate") that combines with oxalacetic acid to form aconitic acid. There is evidence, based on studies with bacteria, that this substance may be acetyl phosphate. In the above equations, the "X" has been assumed to be an OH group, since, no matter what is in the tissues, it must become converted to an OH group by hydrolysis in order that aconitic acid be formed.

At one time it was thought that citric acid formed a part of the tricarboxylic acid cycle, and, indeed, some biochemists used the phrase "citric acid cycle." It is probable that the citric acid formed in metabolism comes from a reversible side reaction of aconitic acid, as shown in the diagram.

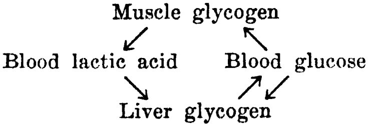
If a careful count is made of the oxygen used, and of the carbon dioxide and water produced, during one complete cycle, it will be found that the over-all reaction can be represented by the equation,

$$CH_3CO{\cdot}COOH + 2\tfrac{1}{2}O_2 \rightarrow 3CO_2 + 2H_2O.$$

In other words, one molecule of pyruvic acid is oxidized completely to carbon dioxide and water in one complete cycle.

Although the tricarboxylic acid cycle first was investigated in connection with carbohydrate metabolism, it is becoming increasingly probable that it is important also in the metabolism of fats and proteins. During the catabolism of fatty acids, some unknown two-carbon compound must be formed (see page 634), and it is possible that it may be identical with the compound formed from pyruvic acid. If this is true, the end stages of fatty acid metabolism could be identical with those of carbohydrate metabolism. It has been known for a long time that a large percentage of the amino acids present in proteins can be converted to carbohydrate, and hence to pyruvic acid, in the body. It is known also that glutamic acid, an amino acid found in proteins (see page 550), can be converted to α-ketoglutaric acid in the tissues. Hence, the tricarboxylic acid cycle may be important in the catabolism of amino acids.

The Lactic Acid Cycle.—Cori has pointed out that the carbon atoms in a lactic acid molecule might be present, in turn, in each of the following types of molecule: blood lactic acid, liver glycogen, blood glucose, and muscle glycogen.



Metabolism of Nerve Tissue.—The brain, spinal cord, and nerves of the body appear to oxidize carbohydrate almost exclusively during nervous activity. Unlike muscle, nerve tissue does not store glycogen, and appears to utilize glucose directly. It is interesting that the pyruvic acid formed in nerve metabolism (and perhaps also that formed in muscle metabolism) cannot be oxidized to carbon dioxide and water unless a coenzyme, called *cocarboxylase* (*thiamine pyrophosphate*), is present. On hydrolysis, cocarboxylase yields thiamine (vitamin B_1) and phosphoric acid.

The end products of carbohydrate metabolism in nerve tissue, and indeed in all other tissues, are carbon dioxide and water.

Energy of Carbohydrate Oxidation.—It will be recalled that a calorie (small calorie or gram calorie) is the amount of heat required to raise the temperature of a gram of water 1° C. (from 14.5° C. to 15.5° C.). In the study of nutrition it is customary to use the large calorie, which is 1,000 small calories, as a unit. Now, of course, all the energy released during metabolism is not in the form of heat energy. However, since all forms of energy can be converted *quantitatively* to heat, it is convenient to measure the energy of metabolism as heat.

The complete oxidation of 1 g. of carbohydrate in the tissues yields about 4 large calories (4,000 small calories) of energy. Seventy-five to 80 per cent of this energy is heat; the remainder is used in causing glands to secrete, nerves to conduct, muscles to contract, and so on. As an engine, then, the body is 20 to 25 per cent efficient, since only this percentage of the total energy production can be used to do useful work. These figures may seem low, but actually they compare favorably with the figures for steam and gasoline engines.

Formation of Fat From Carbohydrate.—Each of us knows that the ingestion of excessive amounts of carbohydrates (sweets) will lead to a deposition of stored fat. The chemical reactions leading to the formation of this fat are unknown. It is possible that the glycerol portion of the fat molecule may be formed by the reduction of glyceric aldehyde, the phosphorylated form of which is produced during muscle contraction. Since the fatty acids present in stored fat contain an even number of carbon atoms in each molecule, it seems reasonable that they may be built up by the condensation of some compound containing two carbon atoms. Conceivably, the unknown two-carbon atom compound might be identical with the compound produced from pyruvic acid (see tricarboxylic acid cycle (page 617).

Lactose Formation.—The sugar present in milk is the disaccharide lactose. Since lactose yields glucose and galactose on hydrolysis, it might be supposed that the mammary gland (breast) removes these monosaccharides from the blood and converts them to lactose. However, it appears that galactose is not required for milk sugar synthesis. During periods of lactation (milk production), the mammary glands remove glucose from the blood and, by some mechanism as yet unknown, convert it to lactose.

Hormonal Control of Carbohydrate Metabolism.—Scattered throughout the body are groups of cells known as endocrine, or ductless, glands (see Chapter XXVIII). These cells manufacture substances, called hormones, which assist in the control and modification of metabolism. Hormones are transported to the various tissues by the blood.

Insulin is manufactured by small groups of cells (the isles of Langerhans) scattered throughout the pancreas. When it is injected into the blood, the level of blood sugar rapidly falls, and the rate of sugar oxidation in the body increases. After a short time it is found that the amount of glycogen in the muscles and in the liver has increased. The functions of insulin appear to be:

(1) To speed up the conversion of blood glucose to muscle glycogen.

(2) To check the breakdown of liver glycogen. Since substances in the blood constantly are being removed and changed to liver glycogen, the amount of glycogen in the liver increases after insulin secretion or injection.

(3) To increase the rate of carbohydrate burning in the body.

The first step in the conversion of glucose to glycogen in the liver appears to be the formation of glucose-6-phosphate. This reaction is catalyzed by an enzyme known as *hexokinase*. Glucose-6-phosphate then rearranges (in the presence of the enzyme *phosphoglucomutase*) to form glucose-1-phosphate. In the presence of the enzyme *phosphorylase* glucose-1-phosphate forms glycogen and phosphoric acid. Dr. C. F. Cori and his associates have reported recently that hexokinase is inhibited by an extract of the anterior lobe of the pituitary gland (see page 698), with the over-all result that the formation of glycogen from glucose is slowed. They reported further that insulin can counteract this inhibition, thus speeding up the formation of glycogen from glucose in the presence of pituitary extract. Although the experiments just cited were carried out *in vitro* (in glass, meaning in laboratory apparatus rather than in the living animal), it is reasonable to suppose that insulin exerts this same effect *in vivo* (i.e., in the living animal). If this is true, one function of the hormone is to regulate the rate of formation of liver glycogen from glucose.

If insulin is not formed in the body in proper amounts, the disease known as diabetes mellitus results (see page 680).

Adrenaline (*epinephrine*) is formed by the medulla (inner portion) of the adrenal glands. One adrenal gland is perched on top of each kidney. Adrenaline causes a rapid breakdown of both liver glycogen and muscle glycogen. As a result of the liver glycogenolysis, the blood sugar level rises. The rate of carbohydrate oxidation increases for a time after adrenalin is injected or secreted.

The pituitary gland is attached to the base of the brain by means of a stalk, called the infundibulum. One of its hormones may stimulate the isles of Langerhans to secrete insulin and so cause an increased deposition of glycogen in the liver. Another pituitary hormone tends to cause an elevation of the blood sugar level, particularly when the animal or person is receiving a diet high in carbohydrate.

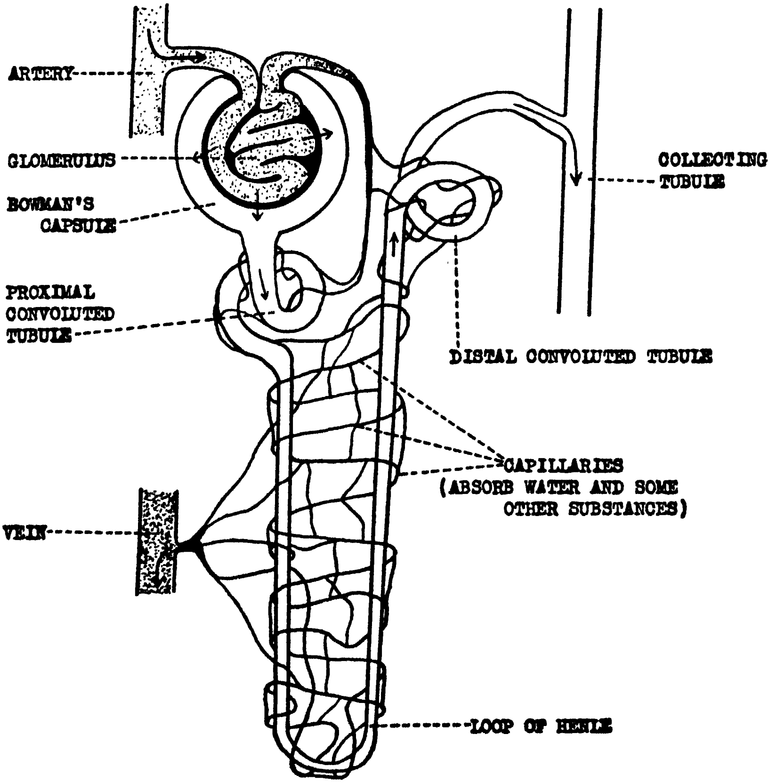


FIG. 68.—Diagram of the functional unit of the kidney (nephron). Explain how urine is formed. (From Arnow: Introduction to Physiological and Pathological Chemistry.)

Thyroxine, the hormone of the thyroid gland (located in the neck), tends to oppose the action of insulin. When too much thyroxine is secreted, carbohydrate utilization is not as efficient as it should be.

The hormone *(cortin)* of the adrenal cortex (outer portion of the gland) also opposes insulin to some extent. When this gland is inactive, or is destroyed by disease, the blood sugar level is lower than normal, and the ability of the liver to synthesize glycogen from amino acids seems to be reduced.

Excretion

The carbon dioxide and water formed by the catabolism of carbohydrates are eliminated from the body as described in Chapter XXIII. There still remains to be discussed the mechanism that normally prevents the escape of the glucose of the blood into the urine.

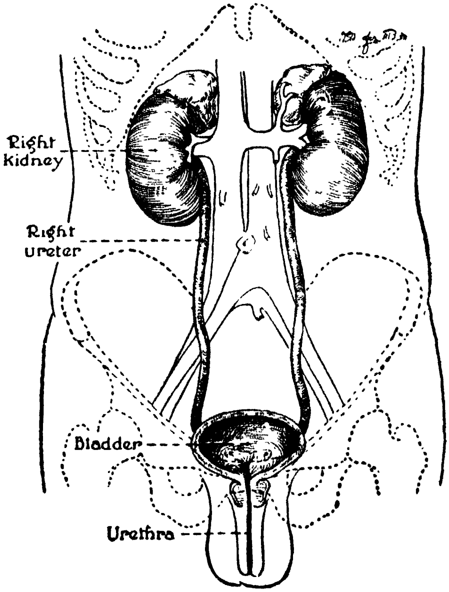


Fig. 69.—The urinary tract of the male. What is the function of this system? (From McClendon and Pettibone: Physiological Chemistry.)

Formation of Urine.—The blood vessels (arteries) entering the kidney break up into smaller and smaller vessels, called arterioles. Each tiny arteriole finally becomes a tiny, thin-walled structure, called a capillary. This capillary is coiled up like a ball of yarn (see Fig. 68), forming a structure known as a glomerulus. Surrounding each glomerulus is a structure (Bowman's capsule) from which there passes out a small tubule. These small tubules from all parts of the kidney join together to form larger collecting tubules. Finally, the collecting tubules empty into a cavity known as the pelvis of the kidney. From the pelvis, urine passes down the ureter to the urinary bladder. The bladder empties itself through a single tubular structure, the urethra.

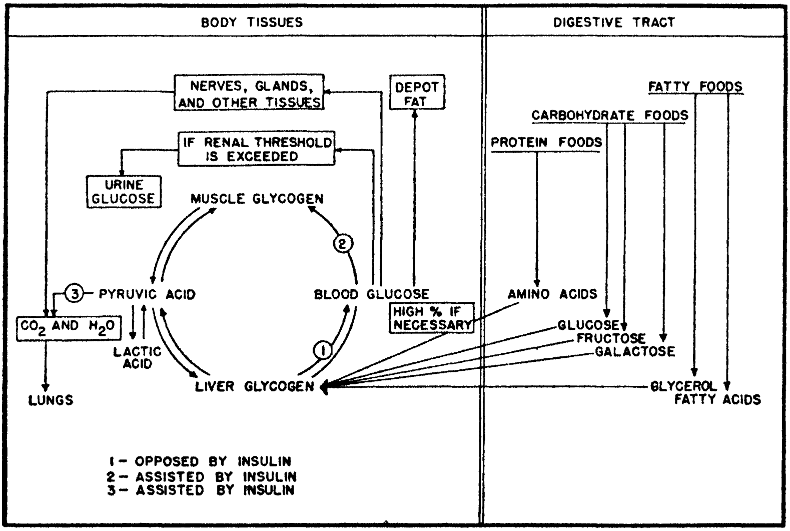


Fig. 70.—Summary of carbohydrate metabolism. What are the final end products of carbohydrate catabolism? (Adapted from Arnow: Introduction to Physiological and Pathological Chemistry.)

The wall of the glomerular capillary is an ultrafilter, or dialyzing membrane. As blood passes through the glomerulus, all the molecules in solution in the plasma, except the protein molecules, can pass across the membrane into Bowman's capsule. As this ultrafiltrate passes down the tubule, however, a part of some of the substances present (especially water, sodium bicarbonate, sodium chloride, and glucose) diffuse back into the blood again. Nearly all the glucose re-enters the blood in this way. The kidney is a rich source of phosphatase, and there is evidence that glucose is converted to glucose-l-phosphate before this absorption occurs. In other words, the absorption of glucose from the kidney tubules seems to resemble its absorption from the intestine.

Some substances (e. g., ammonium salts, hippuric acid) are made by the cells of the tubules and pass out of the body with the urine. Urine that reaches the urinary bladder thus can be described by means of the following word equation:

Urine = Glomerular ultrafiltrate – Substances reabsorbed in the tubules
+ Substances secreted by the tubular cells

Study Questions

1. Define digestion. What are the end products of carbohydrate digestion?
2. What percentage of saliva is water? Name some other substances present in saliva.
3. Name the salivary enzymes important in carbohydrate digestion, and indicate the function of each.
4. What is ptyalin?
5. What is the pH of saliva?
6. Why does salivary digestion cease when swallowed food becomes mixed with gastric juice?
7. Is gastric juice important in the digestion of carbohydrates? Why?
8. List the pancreatic and intestinal enzymes that catalyze carbohydrate digestion. Indicate the function of each.
9. What is the end product of starch digestion? Of glycogen digestion?
10. What are the end products of sucrose digestion? Of lactose digestion? Of maltose digestion?
11. What types of substances are formed from carbohydrates by bacterial activity in the intestine?
12. What fraction of the dry weight of the stools is due to the presence of bacteria?
13. How do you explain the laxative action of ''bulk foods''?
14. Describe the mechanism by means of which monosaccharides are absorbed from the digestive tract.
15. Define intermediary metabolism.
16. What is the fate of fructose in the body? Of galactose?
17. What organs convert fructose to glucose? Galactose to glucose?
18. Define: glycogenesis, glycogenolysis.
19. Name five substances that can form glycogen in the liver.
20. What are the two substances formed by muscle glycogenolysis?
21. What organ is most important in controlling the level of blood glucose?
22. How does the kidney assist in the control of the blood sugar level?
23. What is the average normal value of the fasting blood glucose level?

24. What is meant by the term *renal threshold?* What is the average normal value of the renal threshold for glucose?
25. List the chemical changes that take place during the anaerobic phase of muscle contraction. During the aerobic phase.
26. How does adenylic acid differ from adenosine triphosphate?
27. By what mechanism does dihydroxyacetone phosphate become changed to phosphoglyceric acid during muscle contraction?
28. What change does creatine phosphate undergo during muscle contraction?
29. What inorganic ion is necessary for the maximum efficiency of phosphatase?
30. Can a muscle contract in the absence of oxygen? Can it recover?
31. What is the fate of the pyruvic acid and lactic acid formed during muscle contraction?
32. Make a diagram illustrating the Cori (lactic acid) cycle.
33. In what way does the carbohydrate metabolism of nerve tissue differ from that of muscle tissue?
34. What vitamin is necessary for the oxidation of pyruvic acid in nerve tissue?
35. What are the end products of carbohydrate catabolism?
36. Can fat be formed from carbohydrate in the body? How do you know?
37. What is a large calorie? A small calorie?
38. How many large calories of energy are produced by the oxidation of one gram of carbohydrate in the body?
39. What is the approximate efficiency of the body as an engine?
40. From what sugar does the mammary gland apparently synthesize lactose?
41. What is a hormone?
42. Indicate the function of each of the following hormones in carbohydrate metabolism: insulin, adrenaline, thyroxine, cortin.
43. How does the pituitary gland influence carbohydrate metabolism?
44. By what routes are the carbon dioxide and water formed in carbohydrate metabolism eliminated from the body?
45. Explain how the kidney forms urine.
46. Why is glucose ordinarily not present in appreciable quantities in urine?
47. What is the possible role of phosphatase in the reabsorption of glucose by the kidney tubules?
48. Make a diagram of the tricarboxylic acid cycle.

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CHAPTER XXV

LIPID METABOLISM

Digestion and Absorption

Salivary Lipase.—It has been claimed that small amounts of a lipase (fat-splitting enzyme) can be detected in saliva. It is easy to demonstrate experimentally, however, that the hydrolysis (digestion) of fats in the presence of saliva is too slight to be of any importance in the normal processes of digestion. Perhaps fats adsorbed on the teeth are hydrolyzed slowly.

Gastric Lipase.—Gastric juice contains an enzyme known as gastric lipase. This substance can be obtained by extracting dry gastric mucosa (stomach lining) with dilute alkali, or with water and glycerol. At a pH of 5 (its optimum pH) it digests fats slowly. Moreover, only fats that are emulsified (such as the fat of milk or the fat of egg yolk) are attacked by it. If we remember that gastric juice is almost always more acid than pH 5 (since it contains hydrochloric acid), we are forced to conclude that gastric digestion of fats is of minor, if any, importance.

Bile.—The digestive enzymes are soluble in water or dilute salt solutions, but they are not soluble in fats. The enzymes that are concerned in fat digestion thus can attack the fat only at the surface between the fat particle and the enzyme solution. The total surface of the fat particles (and therefore the rate of fat digestion) is increased enormously if the fat is emulsified (see pages 48 and 52).

Fats that reach the intestinal tract are emulsified by *bile*. Bile is a yellow-brown or green liquid with an intensely bitter taste. It contains sodium bicarbonate and is slightly alkaline (about pH 8) in reaction. After its formation in the liver, bile is stored for a time in the gall bladder, where it loses water to the blood and becomes concentrated. During this storage period, sodium bicarbonate diffuses back into the blood and the pH decreases to a value between 5.5 and 7. When fat enters the small intestine, the gall bladder gradually contracts (see page 703) and its contents enter the duodenum.

The emulsifying power of bile is due to the presence of bile salts. The most important of these are sodium glycocholate and sodium taurocholate (see page 636). These substances lower surface tension and are excellent emulsifying agents.

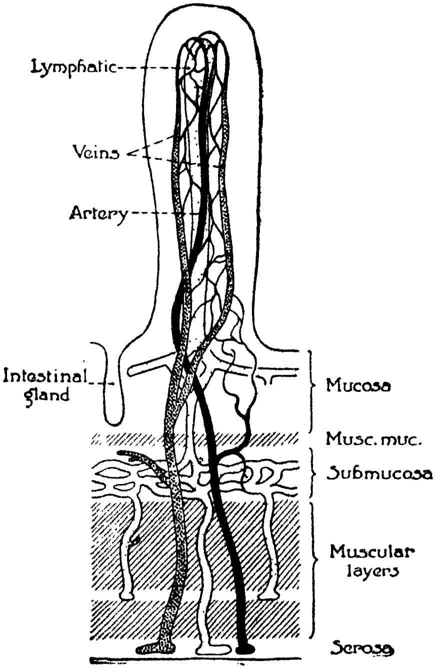


Fig. 71.—An intestinal villus, showing the mechanism for the absorption of digested foods. A villus is a minute, club-shaped structure that projects from the mucous membrane lining the intestine. Which one of the vessels illustrated conveys most of the dietary fat from the intestine to the remainder of the body? (From McClendon and Pettibone: Physiological Chemistry, The C. V. Mosby Co.)

Other substances present in bile are cholesterol, inorganic chlorides and bicarbonates (sodium, potassium, and calcium), and bilirubin. Bilirubin is the chief pigment of the bile. We shall find that it is a catabolic product of hemoglobin metabolism. Biliverdin and bilicyanin, oxidation products of bilirubin, may be present. Cholesterol, the most important animal sterol, sometimes precipitates in the gall bladder, forming cholesterol gallstones. Most gallstones also contain bilirubin, and some of them contain calcium.

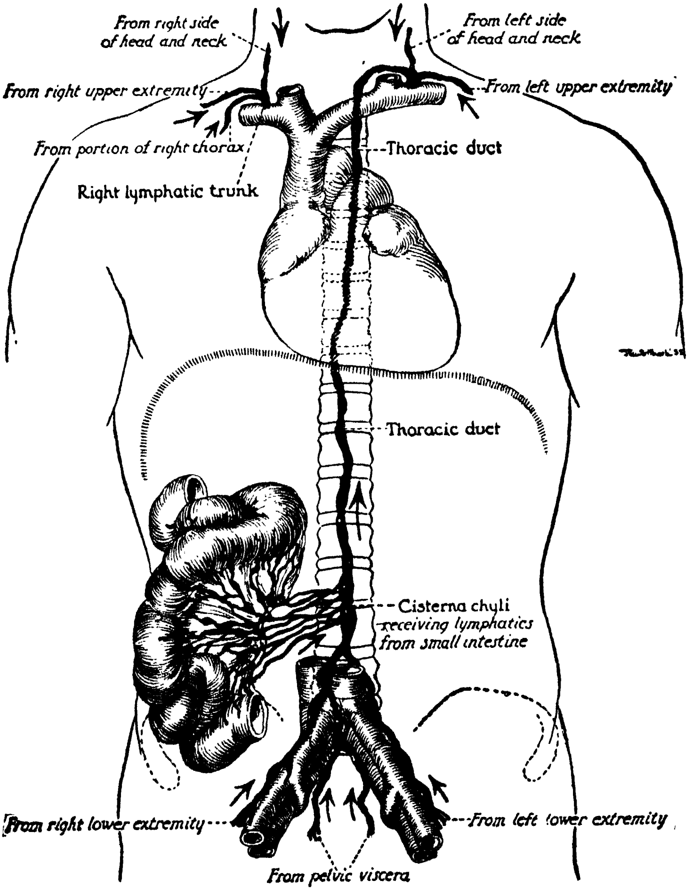

From right side of head and neck
From left side of head and neck
From right upper extremity
From left upper extremity
From portion of right thorax
Right lymphatic trunk
Thoracic duct
Thoracic duct
Cisterna chyli receiving lymphatics from small intestine
From right lower extremity
From left lower extremity
From pelvic viscera

Fig. 72.—Diagram illustrating the circulation of the lymph. How does lymph from the intestine reach the blood stream? (From McClendon and Pettibone; Physiological Chemistry, The C. V. Mosby Co.)

Pancreatic and Intestinal Digestion.—Pancreatic juice contains an enzyme known as *pancreatic lipase,* or *steapsin.* In the presence of bile, this enzyme catalyzes the conversion of emulsified fat to fatty acids and glycerol. Intestinal juice also contains a lipase *(intestinal lipase).*

Absorption.—The end products of fat digestion are glycerol and fatty acids. The glycerol is water soluble; the fatty acids are insoluble in water, but they dissolve readily in the presence of bile salts. These end products diffuse into the mucous membrane (lining) of the intestine. Here they combine again to form fat. Approximately 30 per cent of this fat enters the blood directly. The other 70 per cent diffuses (in emulsified form) into the lymph, or fluid between the body cells. This lymph passes into small lymph vessels (called lacteals in the region of the intestine) which convey it to the blood. The relatively large lymph vessel that drains the intestinal tract is called the thoracic duct. It terminates by emptying into the left subclavian vein in the neck.

There is some evidence that phosphoric acid is necessary for the absorption of glycerol, and perhaps also for the absorption of fatty acids.

Some biochemists believe that appreciable quantities of fat can be absorbed without preliminary digestion.

After a meal rich in fat, microscopic observation of the blood reveals the presence of many emulsified fat droplets *(chylomicrons).* These chylomicrons gradually are removed as the blood circulates through the tissues.

Intermediary Metabolism

Anabolic Products of Fatty Acids.—The chief anabolic products of fatty acids are stored (depot) fat and the lipids necessary for the formation of protoplasm. *Protoplasm* is the material of which the cells are composed.

Depot fat (adipose tissue) is found beneath the skin and around many of the organs of the body. It has several important functions:

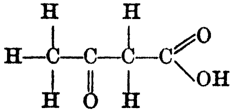
(1) It serves as a reserve food supply. Ordinarily, the body prefers to oxidize carbohydrate for energy purposes. If the carbohydrate stores are used up, or if some pathological condition causes carbohydrate metabolism to be abnormal, depot fat will be oxidized.

(2) The depot fat beneath the skin acts as a heat insulator. Fat is a poor conductor of heat, and adipose tissue assists in preventing a rapid loss of heat from the interior of the body.

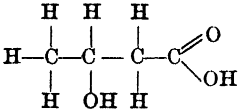
(3) The fat surrounding many organs of the body acts as a support for these organs, and helps to protect them from injury. If these fat cushions are lost because of starvation or disease, some of the body structures (for example, the heart) may function improperly as a result of the loss of support.

The lipids that actually are an integral part of protoplasm are chiefly phospholipids. They are not available for energy purposes, since removal of them would result in the death of the cells.

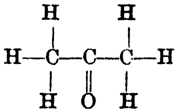
Ketone Bodies.—Acetoacetic acid (diacetic acid), β-hydroxybutyric acid, and acetone are known collectively as the *ketone bodies,* or *acetone bodies.* The first two of these are formed during fatty acid catabolism. Probably acetone should be regarded as a by-product; it is formed by the decarboxylation of (removal of carbon dioxide from) acetoacetic acid.



Acetoacetic acid



β-Hydroxybutyric acid



Acetone

Normally, ketone bodies are present in the blood and urine in very low concentration. However, whenever carbohydrate catabolism is deficient, large amounts of these substances are formed, and increased amounts of them are excreted in the urine. An increased production of ketone bodies is called *ketosis.*

Ketone bodies appear to be manufactured only in the liver, but other tissues (such as muscle) can oxidize them to carbon dioxide and water. We know now that when an animal is unable for some reason to oxidize carbohydrate for energy purposes, ketosis results. For example, ketosis can be produced by starvation, or by feeding a diet high in fat and low in carbohydrate; it accompanies pathological conditions, such as diabetes mellitus, in which carbohydrate metabolism is abnormal. It is evident that the appearance of ketosis under these conditions might be explained by either of the following assumptions:

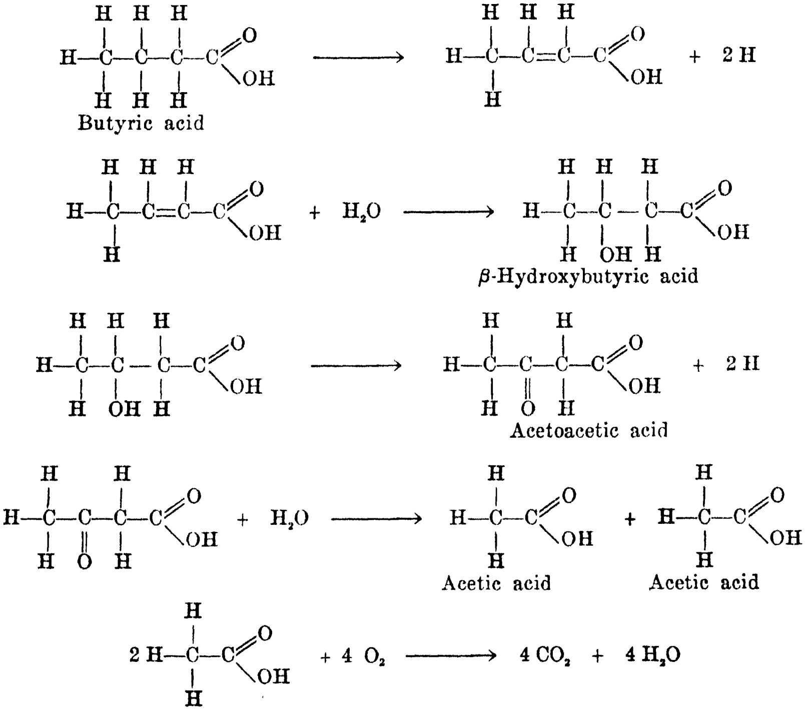
(1) Perhaps the increased amount of ketone bodies in the blood and urine is due to an increased production of them by the liver.

(2) Or, perhaps ketosis results because other tissues are unable to remove ketone bodies from the blood and to catabolize them unless carbohydrate oxidation is proceeding normally in these tissues.

At the present time, most biochemists appear to favor the first assumption (the ''overproduction'' theory of ketosis).

Catabolism of Fatty Acids.—When a gram of fatty acid is oxidized to carbon dioxide and water in the tissues, 9 large calories of energy are produced. This is more than twice the energy derived from the burning of the same quantity of either carbohydrate (4 large calories per gram) or protein (4 large calories per gram).

The fatty acids present in the fat reserves of the body have an even number of carbon atoms per molecule. How are we to explain the formation of molecules containing four carbon atoms (ketone bodies) from such a molecule by oxidation? The most widely accepted explanation is known as the theory of *β-oxidation* (beta-oxidation). According to this theory, oxidation of a fatty acid occurs at the β-carbon atom, with the production of acetic acid and a fatty acid molecule two carbon atoms shorter than the original molecule. Normally, the acetic acid is thought to be oxidized to carbon dioxide and water. Thus, stearic acid (18 carbon atoms) would be converted to palmitic acid (16 carbon atoms) and acetic acid. The palmitic acid then would be converted to myristic acid (14 carbon atoms) and acetic acid. This process, if continued, eventually would result in the formation of a fatty acid containing four carbon atoms in each molecule (butyric acid). The partial oxidation of butyric acid would result in ketone body formation. Finally, under normal conditions at least, the ketone body molecules would be oxidized to carbon dioxide and water. The exact mechanism of this oxidation is not known, but, for our purposes, we may imagine that the oxidation of butyric acid proceeds as indicated by the following equations:



$$\underset{\text{Butyric acid}}{H_3C{-}CH_2{-}CH_2{-}COOH} \longrightarrow H_3C{-}CH{=}CH{-}COOH + 2\,H$$

$$H_3C{-}CH{=}CH{-}COOH + H_2O \longrightarrow \underset{\beta\text{-Hydroxybutyric acid}}{H_3C{-}CH(OH){-}CH_2{-}COOH}$$

$$H_3C{-}CH(OH){-}CH_2{-}COOH \longrightarrow \underset{\text{Acetoacetic acid}}{H_3C{-}CO{-}CH_2{-}COOH} + 2\,H$$

$$H_3C{-}CO{-}CH_2{-}COOH + H_2O \longrightarrow \underset{\text{Acetic acid}}{H_3C{-}COOH} + \underset{\text{Acetic acid}}{H_3C{-}COOH}$$

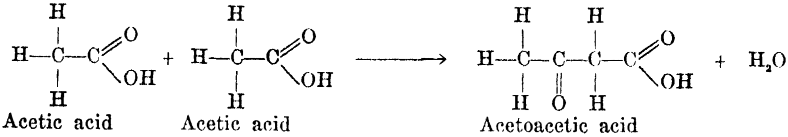
$$2\,H_3C{-}COOH + 4\,O_2 \longrightarrow 4\,CO_2 + 4\,H_2O$$

It is probable that the end result of β-oxidation really is not acetic acid, but rather is some as yet unknown two-carbon atom compound. The possibility that this compound may be oxidized by the tricarboxylic acid cycle already has been mentioned.

The theory of β-oxidation predicts that only one ketone body molecule can be formed from a fatty acid molecule, since all the carbon atoms of the fatty acid except the last four are split off as acetic acid. Under certain experimental conditions, however, it has been found that two or more ketone body molecules may be produced during the burning of a single molecule of fatty acid. Two explanations for this have been offered:

(1) Perhaps some of the acetic acid (or other two-carbon atom) molecules, instead of being oxidized immediately to car-

bon dioxide and water, combine with each other to form acetoacetic acid.



$$CH_3COOH + CH_3COOH \longrightarrow CH_3COCH_2COOH + H_2O$$

(2) Or, perhaps fatty acid molecules can be oxidized at several different points simultaneously *(multiple alternate oxidation).* For example, a palmitic acid molecule (16 carbon atoms) might be oxidized to four butyric acid molecules if oxidation occurred simultaneously at every fourth carbon atom of the molecule. In the same way, multiple alternate oxidation might result in the formation of four molecules of butyric acid and one molecule of acetic acid from a stearic acid molecule (18 carbon atoms).

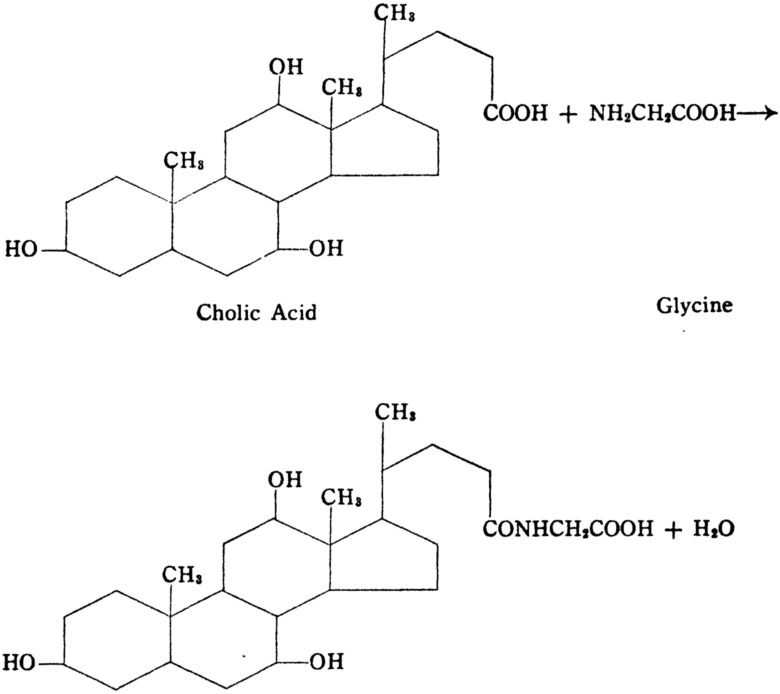
Certain fatty acids with less than eleven carbon atoms per molecule apparently can undergo ω-oxidation (omega-oxidation) in the body. When they are fed to animals, dicarboxylic acids containing the same number of carbon atoms per molecule appear in the urine. It is supposed that the end methyl group of the fatty acid is oxidized to a carboxyl group. The carbon atom of this end methyl group is called the ω-carbon atom.

$$\underset{\text{Pelargonic acid}}{CH_3(CH_2)_7COOH} + 3\,O \longrightarrow \underset{\text{Azelaic acid}}{HOOC(CH_2)_7COOH} + H_2O$$

Function of the Liver in Fatty Acid Metabolism.—The liver is the site of formation of the bile acids, whose salts are necessary for the proper digestion of lipids and for the absorption of fatty acids from the intestinal tract. Glycocholic acid is formed from cholic acid and glycine.

Taurine, $NH_2CH_2CH_2SO_2OH$, is believed to be formed in the body from cystine or methionine. In the liver it combines with cholic acid to form taurocholic acid. Water is split out between the COOH group of the cholic acid and the NH_2 group of the taurine.

Cholic acid is thought to be formed in the liver, but the dietary substances required for its synthesis are not known. Probably only small amounts are manufactured each day, because most of the bile salts that reach the intestine are reabsorbed and returned to the liver by the blood.



Cholic Acid

Glycine

Glycocholic Acid

The formation and removal of phospholipids are more rapid in the liver than in other organs. In general, the fatty acids of the phospholipids are more unsaturated (contain more double bonds) than the fatty acids of the dietary fat. Probably the more unsaturated fatty acids of the food are used in the synthesis of this material. Lipids are not soluble in water, but phospholipids form stable emulsions, and are transported readily by the blood.

The formation of ketone bodies and the manufacture of fat from carbohydrate and protein are important functions of the liver.

Oxidation of Fatty Acids in Muscle.—We have no direct proof that fatty acids can be oxidized by muscles, but we have good reasons for supposing that such a reaction can take place.

(1) If blood, or a specially prepared nutrient solution, containing ketone bodies is allowed to pass through a muscular organ (such as the heart) isolated from the body, but still alive, it is found that the ketone bodies disappear. At the same time, oxygen is used and carbon dioxide is eliminated. It seems reasonable to suppose that the ketone bodies that disappear during the experiment are oxidized by the muscle.

(2) When a food is oxidized in the body, carbon dioxide is eliminated and oxygen is used. The number obtained by dividing the volume of carbon dioxide formed by the volume of oxygen utilized in a given time by an organ or tissue is called the *respiratory quotient (R. Q.).*

$$\text{R. Q.} = \frac{\text{Volume of } CO_2 \text{ produced}}{\text{Volume of } O_2 \text{ used}}$$

On the average, for each 71 cc. of carbon dioxide formed during the oxidation of fat, 100 cc. of oxygen are used. The R. Q. for fat is thus 0.71. For carbohydrate it is 1.0; for protein, about 0.83. If a piece of muscle is removed from a starving animal and placed in a suitable nutrient fluid, its R. Q. is found to be close to 0.71. This finding makes it seem probable that muscles can oxidize fat with the production of carbon dioxide and energy.

Question of Conversion of Fat to Carbohydrate.—It has been proved beyond doubt that glycerol can be converted to glycogen by the liver. It is likely also that fatty acids with an odd number of carbon atoms per molecule can be changed to liver glycogen. Probably, however, the ingestion of fatty acids containing even numbers of carbon atoms per molecule cannot result in an increase in the carbohydrate stores of the body. It is true that such fatty acids can, in part at least, be converted to carbohydrate by means of the tricarboxylic acid cycle (see page 618). However, if the reactions making up the tricarboxylic acid cycle are studied, it will be apparent that the conversion of fatty acid metabolites to carbohydrate involves a simultaneous loss of other carbohydrate molecules, and hence the total amount of carbohydrate does not increase.

Source of Milk Fat.—Milk fat (butter) differs from other body fats in its content of lower fatty acids. About one-third of the fatty acid content of milk fat is due to the presence of fatty acids containing less than 16 carbon atoms per molecule.

If the fat content of the blood entering a lactating (milk-producing) mammary gland is compared with that of the blood leaving the same gland, it is found that just sufficient fat to account for the fat of the milk formed is removed from the blood. In other words, the fat of the blood can be converted to milk fat during lactation. The blood phospholipids apparently cannot be used for milk fat synthesis.

Functions of Phospholipids.—Very little is known about the metabolic functions of the phospholipids. *Sphingomyelins* are found principally in the white myelin sheaths that surround certain nerves of the body; they are thought to be necessary for the formation of these sheaths. *Lecithins* and *cephalins* form stable emulsions in water and possibly are important in the transport of fatty acids from one tissue to another. They are essential components of protoplasm, and indeed, *the formation of protoplasm is the only universally recognized function of the lecithins.* Cephalins play a role in blood clotting (see page 653).

Cholesterol Metabolism.—Cholesterol, in contrast to most sterols, readily is absorbed from the intestinal tract. It is found in the blood and in all the cells of the body. In the blood it exists partly in free form and partly in the form of fatty acid esters.

Cholesterol can be made in the body; it is not a necessary component of the diet. It has been estimated that adults manufacture 3 to 5 grams of it each day. We do not yet know what dietary materials are necessary for its synthesis, although recently it has been shown with the aid of a carbon isotope that the carbon atoms of acetic acid can be incorporated into the cholesterol molecule.

Much of the cholesterol that reaches the intestine by way of the bile is reabsorbed, but some of it passes down the digestive tract with the products of digestion. During this passage through the intestine, about three-fourths of the cholesterol is reduced to *coprosterol* (dihydrocholesterol) by bacterial action. The coprosterol and the unchanged cholesterol are eliminated from the body in the stools.

Endocrine Control of Fat Metabolism.—When the thyroid gland is underactive, the rate of metabolism decreases, and there is a storage of depot fat. The lipid content of the blood is higher than normal. Overactivity of this gland gives a reverse picture: fat storage is decreased and the level of blood lipids is lower than normal.

The pituitary gland forms a substance that stimulates the formation of ketone bodies. Another pituitary hormone appears to cause a transfer of depot fat to the liver. In some cases of overactivity of this gland, increased storage of depot fat occurs.

The sex glands have some influence on fat deposition. Underactivity of these glands sometimes leads to an abnormal type of fat deposition.

Obesity.—*Obesity* is a term used to indicate the storage of excessive amounts of fat in the tissues. In other words, *obese* people are *fat* people. In a small percentage of cases obesity is due to some abnormality of metabolism, or to a disorder of the endocrine glands. However, the great majority of fat people become obese because *they eat more energy-yielding food than they burn up in their tissues.* Obese persons frequently complain that they eat no more than their acquaintances of normal weight. This may be true, because the *amount* of food eaten is not always of major importance. One-third ounce of butter, two ounces of green Lima beans, and one pound of lettuce all have the same caloric value. Most fat people prefer foods of high energy content.

People tend to become obese as they grow older. There are two important reasons for this: (1) as people grow older, they exercise less and so require less food for energy purposes; and (2) the rate at which food is metabolized in the body becomes progressively less with advancing age. It follows that an elderly person will become obese if he eats the normal diet of a young adult.

Excretion

Carbon dioxide and water are the normal end products of fatty acid and glycerol catabolism. They are eliminated from the body as described elsewhere (see Chapter XXIII).

Normally, the excretion of ketone bodies in the urine does not exceed 10 to 20 mg. each day. However, in severe ketosis as much as 100 grams of acetone, acetoacetic acid, and β-hydroxybutyric acid may be present in a twenty-four-hour sample of urine.

Ten to 20 per cent by dry weight (2 to 4 per cent by moist weight) of the stools is due to the presence of lipids. This lipid mixture resembles that of the blood, and its composition is not influenced very much by the diet. Most of its appears to be excreted into the small intestine from the blood. Approximately one-half of it is neutral fat; the remainder is a mixture of free fatty acids, soaps, phospholipids, and sterols.

Study Questions

1. Is salivary digestion of fats of any importance? Explain.
2. What type of food fat can be digested by gastric lipase?
3. How important is the digestion of fat by gastric juice? Explain.
4. Does bile contain digestive enzymes?
5. Explain why emulsified fats are digested more rapidly than non-emulsified ones.
6. What is the pH of bile as it leaves the liver? As it enters the small intestine?
7. Name the principal bile salts. What are their functions?
8. Make a list of the various substances found in bile.
9. What enzymes catalyze the digestion of fats in the small intestine?
10. What are the end products of fat digestion?
11. Describe the absorption of the end products of fat digestion.
12. Approximately what percentage of digested fat enters the blood directly?
13. What are chylomicrons?
14. What are the chief anabolic products of fatty acids?
15. Describe the functions of depot fat.
16. Can all the lipid of the body be used for energy purposes in time of need? Explain.
17. Name the ketone bodies, and give the structural formula of each.
18. By what type of chemical reaction is acetone formed in the body?
19. Under what circumstances are large amounts of ketone bodies present in the blood and urine?

20. What is meant by the term *ketosis?*
21. What organ manufactures ketone bodies?
22. What theories have been advanced to explain the appearance of ketosis? Which one of these probably is correct?
23. How many large calories of energy are produced by the oxidation of one gram of each of the following in the body: fat, carbohydrate, protein?
24. Explain what is meant by the theory of β-oxidation.
25. What two theories have been advanced to explain the production of more than one mole of ketone body from a mole of fatty acid in the body?
26. What is meant by ω-oxidation? Would you expect palmitic acid to undergo this type of oxidation in the body? Why?
27. List the functions of the liver in fatty acid metabolism.
28. What are the products of hydrolysis of glycocholic acid? Of taurocholic acid?
29. What organ is believed to manufacture cholic acid?
30. What findings suggest that the liver may be important in beginning the catabolism of fatty acids?
31. What evidence indicates that fatty acids can be burned in muscle tissue?
32. Define respiratory quotient. What is the R. Q. for the complete oxidation of fat in the body? What is it for the oxidation of protein and carbohydrate in the body?
33. What is known about the conversion of fat to carbohydrate in the body?
34. What is the source of milk fat? How does milk fat differ chemically from the other tissue fats?
35. List the known functions of the various phospholipids.
36. Is cholesterol readily absorbed from the intestinal tract? Is this true of most sterols?
37. Can cholesterol be made in the body?
38. What is coprosterol? How does it gain entrance into the intestinal tract? By what route is it eliminated from the body?
39. How is fat metabolism influenced by each of the following endocrine glands: thyroid, pituitary, gonads (sex glands)?
40. What is the most common cause of obesity?
41. Why do many people tend to become obese as they grow older?
42. Explain the statement that "the amount of food eaten is not always of major importance in the development of obesity."
43. Approximately how many milligrams of ketone bodies are present in a twenty-four-hour sample of normal urine? Is this amount increased very much if the patient has a severe ketosis?
44. What are the usual end products of fat catabolism? How are they eliminated from the body?

45. What types of lipid are found in the stools? What percentage of the weight of the stools is due to their presence? What is the most important source of the lipid of the stools?

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CHAPTER XXVI

PROTEIN METABOLISM

Digestion and Absorption

Salivary Proteinase.—Saliva contains small amounts of a proteinase (protein-digesting enzyme), but it is unlikely that this enzyme plays any significant role in protein digestion.

Gastric Digestion.—Gastric (stomach) juice, when freshly secreted, ordinarily has a pH of about 1. This relatively high acidity is due to the presence of hydrochloric acid. However, some apparently normal people (about 5 per cent of young adults and perhaps 20 to 30 per cent of elderly adults) secrete a gastric juice free of this acid. When food is swallowed, the pH of the stomach contents may rise to 3 or 4, because the proteins and other food buffers combine with much of the hydrochloric acid. In addition to its antiseptic properties (HCl destroys many of the microorganisms swallowed with the food), hydrochloric acid is necessary for the formation of active pepsin from inactive pepsinogen (see below).

Pepsinogen is a protein secreted by the glands of the gastric mucosa (stomach lining). In the presence of hydrochloric acid (or, for that matter, of other acids), it becomes an active proteinase, *pepsin*. Pepsin has been isolated in crystalline form. It is an albumin. Its optimum pH varies with the substrate used, but it is in the neighborhood of pH 2 in most cases. In the presence of pepsin, food proteins are converted to *proteoses* and *peptones*.

Rennin is an enzyme found in the stomach of the calf and of the kid. It catalyzes the change of casein, the principal protein of cow's milk, to paracasein. In the presence of calcium salts, calcium paracaseinate then is formed. This substance is insoluble and precipitates. Crude extracts of calf stomach containing rennin are known as *rennet*. Dietitians often employ rennet in preparing milk foods and custards.

Many textbooks state that rennin occurs in the stomach of human beings. However, there is no convincing evidence for

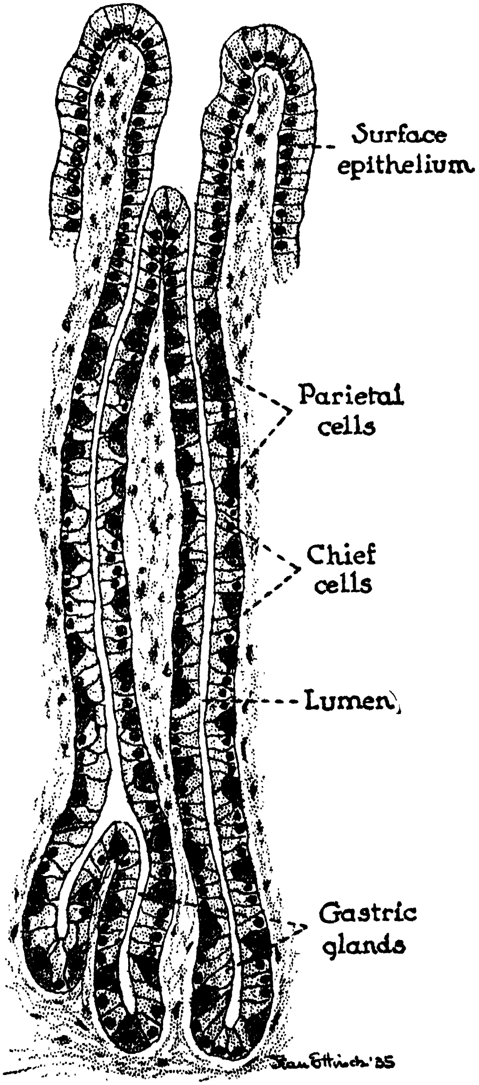
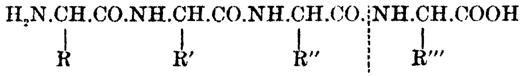


Fig. 73.—A microscopic section of the lining of the stomach to show the gastric (stomach) glands. Hydrochloric acid is secreted by the parietal cells; pepsinogen is secreted by the chief cells. What is the function of pepsin? (From McClendon and Pettibone: Physiological Chemistry, The C. V. Mosby Co.)

this statement, and, indeed, there is considerable evidence to the contrary. Human gastric juice will clot milk, as do extracts containing rennin, but this clotting appears to be caused by the pepsin present in the juice.

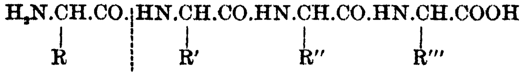
Pancreatic Digestion.—*Trypsinogen* and *chymotrypsinogen* are proteins present in pancreatic juice. When this digestive fluid enters the small intestine, a substance in it *(prokinase)* becomes converted to *enterokinase.* Enterokinase then reacts in some unknown manner with trypsinogen, forming an active proteinase, *trypsin.* Chymotrypsinogen is converted to an active proteinase, *chymotrypsin,* by trypsin. Trypsin and chymotrypsin (as well as their proenzymes trypsinogen and chymotrypsinogen) have been isolated in crystalline form. These enzymes catalyze the conversion of proteins, proteoses, and peptones to *peptides.* The pure enzymes are most active in slightly alkaline solution, but it has been claimed that pancreatic juice digests proteins most efficiently in slightly acid solution in the presence of bile.

Pancreatic juice contains a mixture of peptidases. This mixture formerly was called *pancreatic erepsin.* All of the polypeptidases present are *carboxypolypeptidases;* that is, they attack (split off) the amino acid on the carboxyl end of a polypeptide chain. For example, the following peptide would undergo hydrolysis at the peptide linkage indicated by the dotted line. *Dipeptidases* (enzymes that catalyze the hydrolysis of dipeptides) also are present in pancreatic juice.



$$\mathrm{H_2N.\underset{\mid \atop R}{CH}.CO.NH.\underset{\mid \atop R'}{CH}.CO.NH.\underset{\mid \atop R''}{CH}.CO.\vdots NH.\underset{\mid \atop R'''}{CH}.COOH}$$

Intestinal Digestion.—*Intestinal erepsin* is the term formerly applied to the mixture of peptidases secreted by the intestinal mucosa. The intestinal polypeptidases are *aminopolypeptidases;* i.e., they split polypeptides at the linkage indicated below by the dotted line:

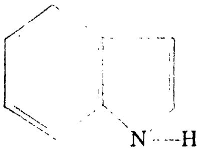


$$\mathrm{H_2N.\underset{\mid \atop R}{CH}.CO.\vdots HN.\underset{\mid \atop R'}{CH}.CO.HN.\underset{\mid \atop R''}{CH}.CO.HN.\underset{\mid \atop R'''}{CH}.COOH}$$

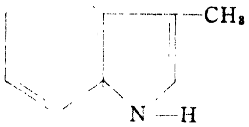
Dipeptidases also are present.

Enzymes concerned with the hydrolysis of the nucleic acid of nucleoproteins are secreted into the intestine. The conversion of nucleic acid to nucleotides is catalyzed by *polynucleotidase*. *Nucleotidase* catalyzes the formation of phosphoric acid and nucleosides from nucleotides. Nucleosides are split to pentose and purines (or pyrimidines, as the case may be) by the catalytic action of *nucleosidase*.

Intestinal Putrefaction.—A small percentage of the protein of the diet is not digested and absorbed, and intestinal bacteria decompose this material, forming peptides, amino acids, ptomaines (amines), mercaptans, and phenolic compounds. *Indole* and *skatole* are responsible for most of the odor of the stools; they are formed from tryptophan.

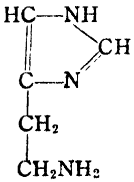


Indole

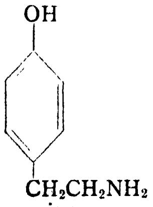


Skatole

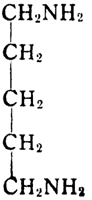
Histamine is formed from histidine; *tyramine*, from tyrosine; *cadaverine*, from lysine; and *putrescine*, from arginine.



Histamine

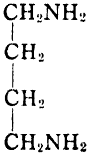


Tyramine



$$CH_2NH_2-CH_2-CH_2-CH_2-CH_2NH_2$$

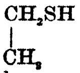
Cadaverine



$$CH_2NH_2-CH_2-CH_2-CH_2NH_2$$

Putrescine

Ethyl mercaptan, methyl mercaptan, **and** ***hydrogen sulfide*** are formed from cystine.



$$CH_2SH-CH_3$$

Ethyl mercaptan

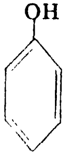
CH_3SH

Methyl mercaptan

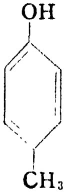
H_2S

Hydrogen sulfide

Various *phenols* and *cresols* are formed from tyrosine.

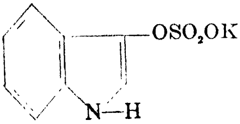


Phenol



Cresol

Small amounts of these substances are absorbed from the intestinal tract. In most cases, they undergo various changes in the tissues (particularly in the liver) that result in the formation of detoxified (nonpoisonous) substances. These detoxified products are excreted in the urine. For example, indole is changed to urinary indican in the liver; the urinary indican thus formed leaves the body in the urine.



Urinary indican

Absorption.—The end products of protein digestion are amino acids and, perhaps, peptides sufficiently soluble to be absorbed before they can be hydrolyzed to amino acids. These end products pass directly from the intestinal tract into the blood stream by simple diffusion.

Intermediary Metabolism

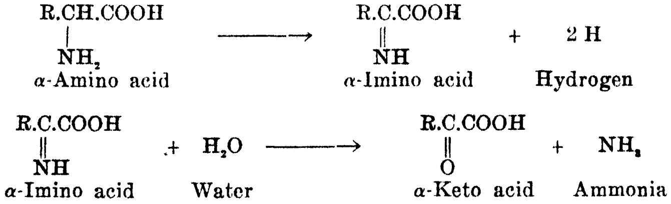
Anabolic Products of Amino Acids.—About 80 per cent of the solid material of the body cells is protein. This body protein constantly is breaking down and re-forming again. Most of the amino acids and soluble peptides entering the blood from the intestinal tract quickly become incorporated, for a time at least, into the tissue protein molecules. Eventually they find their way back into the blood. Even during periods of fasting, blood plasma contains 4 or 5 mg. of α-amino acid nitrogen per 100 cc. If the average molecular weight of the amino acids is assumed to be 125, this amount of α-amino acid nitrogen corresponds to from 35 to 45 mg. of amino acids.

Some of the amino acids of the blood can be converted to glycogen in the liver. Such amino acids are termed *antiketogenic* amino acids, because they oppose ketosis by increasing the carbohydrate store of the body. Glycine, alanine, serine, cysteine, aspartic acid, glutamic acid, arginine, proline, and hydroxyproline are antiketogenic acids. Since depot fat can be formed from carbohydrate (see page 620), it follows that some of the amino acids of the diet eventually may be converted to fat.

Under certain conditions, at least, leucine, histidine, phenylalanine, and tyrosine can form ketone bodies in the liver.

All the enzymes, and some of the pigments and hormones, of the body are proteins. They are made in the tissues from the amino acids present in the blood and other tissue fluids.

Amino Acid Catabolism in the Liver.—The liver contains enymes that catalyze the *oxidative deamination* of amino acids. That is to say, in the presence of oxygen these enzymes cause the formation of α-keto acids and ammonia.

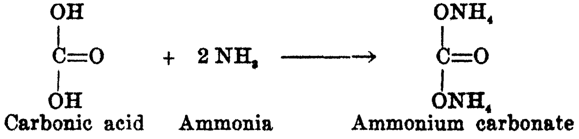


$$\begin{array}{c}\mathrm{R.CH.COOH}\\ |\\ \mathrm{NH_2}\\ \alpha\text{-Amino acid}\end{array} \longrightarrow \begin{array}{c}\mathrm{R.C.COOH}\\ \|\\ \mathrm{NH}\\ \alpha\text{-Imino acid}\end{array} + \begin{array}{c}\mathrm{2\,H}\\ \text{Hydrogen}\end{array}$$

$$\begin{array}{c}\mathrm{R.C.COOH}\\ \|\\ \mathrm{NH}\\ \alpha\text{-Imino acid}\end{array} + \begin{array}{c}\mathrm{H_2O}\\ \text{Water}\end{array} \longrightarrow \begin{array}{c}\mathrm{R.C.COOH}\\ \|\\ \mathrm{O}\\ \alpha\text{-Keto acid}\end{array} + \begin{array}{c}\mathrm{NH_3}\\ \text{Ammonia}\end{array}$$

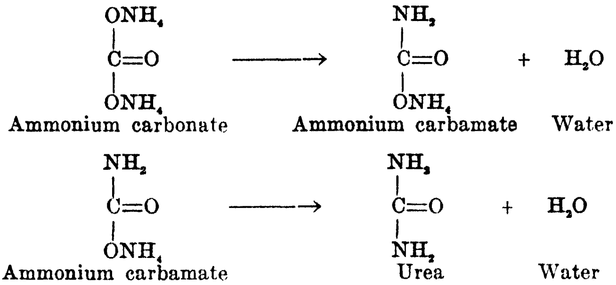
The keto acids thus formed may be oxidized to carbon dioxide and water with the production of energy, or they may be used to synthesize glycogen and other anabolic products.

The ammonia produced by the oxidative deamination of amino acids is converted to *urea,* $NH_2.CO.NH_2$, in the liver. Several theories have been advanced to account for this formation. According to one of them, ammonia reacts with carbonic acid (carbon dioxide and water), forming ammonium carbonate.



$$\begin{array}{c}\mathrm{OH}\\ |\\ \mathrm{C{=}O}\\ |\\ \mathrm{OH}\\ \text{Carbonic acid}\end{array} + \begin{array}{c}\mathrm{2\,NH_3}\\ \text{Ammonia}\end{array} \longrightarrow \begin{array}{c}\mathrm{ONH_4}\\ |\\ \mathrm{C{=}O}\\ |\\ \mathrm{ONH_4}\\ \text{Ammonium carbonate}\end{array}$$

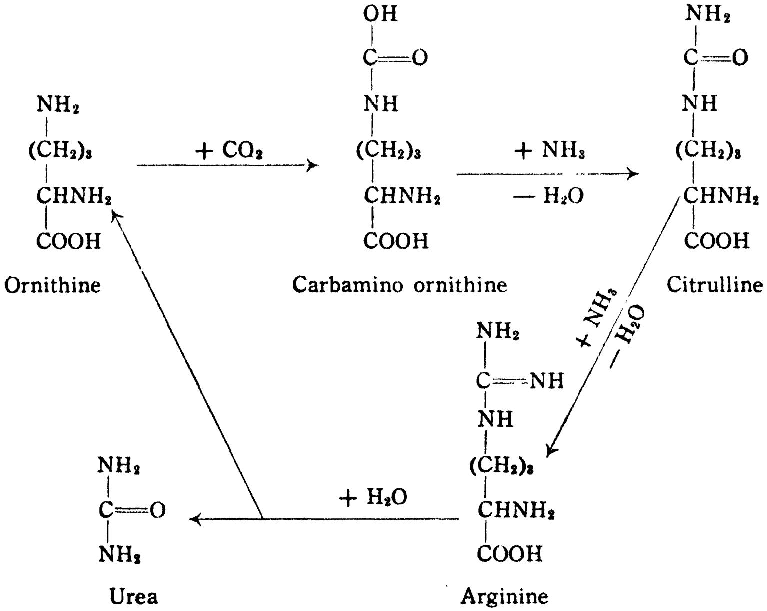
The ammonium carbonate is converted to urea by the removal of water.



$$\begin{array}{c}\mathrm{ONH_4}\\|\\\mathrm{C{=}O}\\|\\\mathrm{ONH_4}\end{array} \longrightarrow \begin{array}{c}\mathrm{NH_2}\\|\\\mathrm{C{=}O}\\|\\\mathrm{ONH_4}\end{array} + \mathrm{H_2O}$$

$$\begin{array}{c}\mathrm{NH_2}\\|\\\mathrm{C{=}O}\\|\\\mathrm{ONH_4}\end{array} \longrightarrow \begin{array}{c}\mathrm{NH_2}\\|\\\mathrm{C{=}O}\\|\\\mathrm{NH_2}\end{array} + \mathrm{H_2O}$$

Another postulated mechanism is more complicated. It is known as the *ornithine cycle.* The essential reactions are indicated in the following diagram:

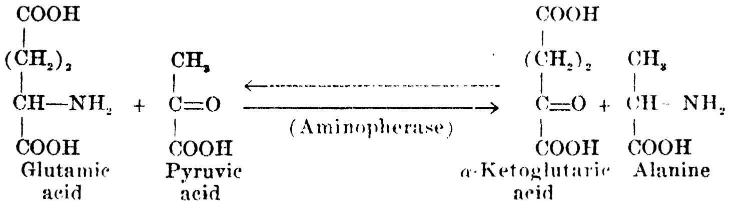


The urea formed in the liver diffuses into the blood, which transports it to the kidneys. It is eliminated from the body in the urine. Approximately 20 to 40 mg. of urea are present in 100 cc. of normal blood.

Urea, then, is one of the end products of the amino acid catabolism of most animals. The other end products are carbon dioxide and water. Birds and reptiles convert ammonia to *uric acid* instead of urea. The mechanism of this conversion is unknown.

Transamination.—As we have seen, keto acids are formed during the metabolism of carbohydrates, fatty acids, and amino acids. Certain of these keto acids can react reversibly with glutamic acid or aspartic acid to form new amino acids. This reaction, which involves the transfer of an amino group from one compound to another, is called *transamination*. *Aminopherase* is the specific enzyme that catalyzes the amino group exchange. This enzyme, or mixture of enzymes, is present in most of the body tissues.

The formation of an α-amino acid from a keto acid is illustrated by the following reaction, in which alanine is formed from pyruvic acid:



$$\mathrm{COOH{-}(CH_2)_2{-}CH(NH_2){-}COOH} + \mathrm{CH_3{-}CO{-}COOH} \xrightleftharpoons[\text{(Aminopherase)}]{} \mathrm{COOH{-}(CH_2)_2{-}CO{-}COOH} + \mathrm{CH_3{-}CH(NH_2){-}COOH}$$

When the concentration of monocarboxy α-amino acid is high and the concentration of monocarboxy keto acid is low, the reaction goes in the reverse direction, as indicated by the dotted arrow. Under these circumstances, monocarboxy amino acids are changed to keto acids. This type of deamination (removal of amino groups) does not require oxygen, and does not result in the formation of ammonia.

It should be noted that two of the acids given in the above equation (pyruvic acid and α-ketoglutaric acid) have been mentioned in connection with the tricarboxylic acid cycle (page 617).

Energy of Protein Catabolism.—If we examine the formula for urea, $NH_2.CO.NH_2$, we notice that the nitrogen is present in amino groups, just as it is in amino acid molecules. In other words, the oxidation of amino acids in the tissues does not involve the oxidation of the nitrogen present in them. However, the oxidation of the remainder of the amino acid molecule results in the formation of carbon dioxide and water, and energy is released. On the average, the oxidation of a gram of protein in the tissues produces 4 large calories of energy.

Plasma Proteins.—Each 100 cc. of normal plasma (the liquid portion of the blood) contains about 7 grams of protein. Approximately 60 per cent of this protein is *serum albumin* and 35 per cent is *serum globulin.* The other 5 per cent is made up chiefly of *fibrinogen.* Small amounts of *prothrombin* also are present.

There is a considerable amount of evidence that some of these proteins are manufactured in the liver.

At one time it was believed that the plasma proteins could be used neither for the synthesis of tissue proteins nor for energy production in the body. The work of recent years has shown conclusively that this belief was incorrect. It is possible to supply the protein needs of animals by injecting plasma protein solutions into their blood streams, even when no protein is present in the diet.

One of the functions of the plasma proteins, particularly serum albumin, is to assist in the regulation of the exchanges of water between the blood capillaries and the tissue fluid (lymph). Fig. 74 is a diagram of a blood capillary. At the arterial end of the capillary, the blood pressure is about 32 mm. of Hg; at the venous end, it amounts to approximately 12 mm. of Hg. This pressure tends to force fluid out of the blood and into the tissue spaces. The tissue fluid (lymph) outside the capillary contains only small amounts of protein, since the capillary wall is a dialyzing membrane. This difference in concentration of protein on the two sides of the membrane tends to cause fluid to move from the tissue spaces into the blood, because the colloid (protein) osmotic pressure of the blood is higher than that of the tissue fluid. This difference in osmotic pressure amounts to about 20 mm. of Hg. Fluid thus passes from the capillary to the tissues at the arterial end, since the blood pressure there is higher than the colloid osmotic pressure. At the venous end, where the colloid osmotic pressure exceeds the blood pressure, fluid passes in the reverse direction. In other words, under normal conditions fluid leaves the capillary at its arterial end, passes into the tissue spaces, and enters the capillary again at its venous end. Small amounts of the tissue fluid, instead of passing directly into the blood, enter lymph vessels (lymphatics) and thus reach the blood by a roundabout route (see page 630). The mechanism just described makes it

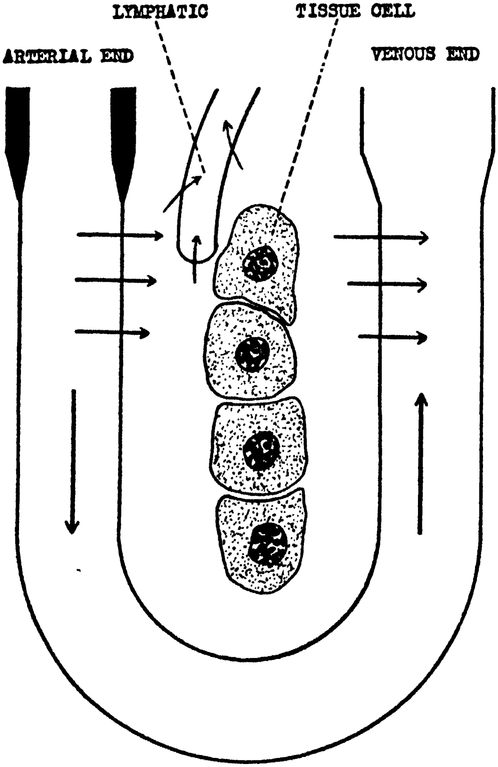


Fig. 74.—Diagram of a capillary loop. Explain how plasma proteins assist in regulating the movement of fluid across the walls of capillaries. (From Arnow: Introduction to Physiological and Pathological Chemistry, The C. V. Mosby Co.)

possible for soluble food molecules and gases in the blood to reach the tissue cells, and for waste products formed by the cells to be removed.

In most cases, when harmful bacteria or their toxins (poisons) enter the body, *antibodies* soon appear in the blood. These antibodies are proteins that assist in destroying the bacteria and their toxins. Blood antibodies always appear to accompany the serum globulin; that is, if the various blood proteins are separated from each other, the blood antibodies will be found to be concentrated in the serum globulin fraction. This suggests that one of the functions of the serum globulin fraction of the plasma protein is to defend the body against invasion by pathogenic (disease-producing) bacteria.

Fibrinogen and *prothrombin* are globulins, although they are not usually considered to be a part of what we have called the serum globulin fraction of the plasma protein. *They are necessary for blood clotting.* When bleeding occurs, tiny fragments of tissue in the blood, called *blood platelets* or *thrombocytes,* disintegrate and release a material known as *thromboplastin.* Thromboplastin probably is a conjugated protein; at any rate, *cephalin* (one of the phospholipids; see page 286) is present in it. In the presence of the calcium ions of the blood and thromboplastin, prothrombin is converted to a protein called *thrombin.*

$$\text{Prothrombin} + \text{Ca}^{++} + \text{Thromboplastin} \longrightarrow \text{Thrombin}$$

Thrombin then catalyzes the change of the soluble fibrinogen to an insoluble protein, *fibrin.*

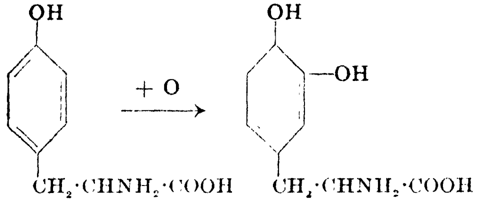
$$\text{Thrombin} + \text{Fibrinogen} \longrightarrow \text{Fibrin}$$

Fibrin precipitates as a meshwork of needle-shaped fibers. This meshwork, together with the blood cells and fluid trapped within it, forms the blood clot.

Prothrombin cannot be produced by the liver in the absence of vitamin K (see page 732).

A complex organic substance known as *heparin* has been isolated from various tissues. Small amounts of it occur in the blood. It inhibits blood clotting, and it has been suggested that its presence in the blood prevents clotting within the blood vessels. The amount present is insufficient to prevent clotting when large numbers of platelets disintegrate, however, as they do when bleeding occurs, or when blood is removed from the body.

Melanin Metabolism.—*Melanin* is the brown pigment of the skin and hair. Small amounts of it are found also in the retina (inner lining) of the eye, in certain glands, and in the nervous system. It is thought to be formed in the body from tyrosine. Certain enzymes, called *tyrosinases*, found in plants and lower animals, catalyze the oxidation of tyrosine to dihydroxyphenylalanine. This latter compound also is known as dioxyphenylalanine or dopa (DiOxyPhenylAlanine).



Tyrosine Dopa

Tyrosinases have not been proved to be present in the normal tissues of the higher animals, including man, but the foregoing reaction is believed to be the first step in melanin synthesis. Perhaps it occurs without the assistance of an enzyme, since, in the presence of minute quantities of iron, hydrogen peroxide converts tyrosine to dopa. As we have seen (see Chapter XXIII), hydrogen peroxide and iron are present in the tissues.

Dopa is converted to melanin in the presence of oxygen and an enzyme known as *dopa oxidase*. Dopa oxidase occurs in special cells (melanoblasts) located in the lower layers of the skin and in the cells from which the hairs grow.

Melanin is a brown pigment, although concentrated solutions or suspensions of it appear black. It is readily soluble in alkalies, but precipitates from acid solution. Apparently its molecule is very large, for it is incapable of passing through dialyzing membranes. Only small amounts of it are required for intense coloration; indeed, it has been estimated that the entire skin of a Negro contains less than 1 g. of melanin.

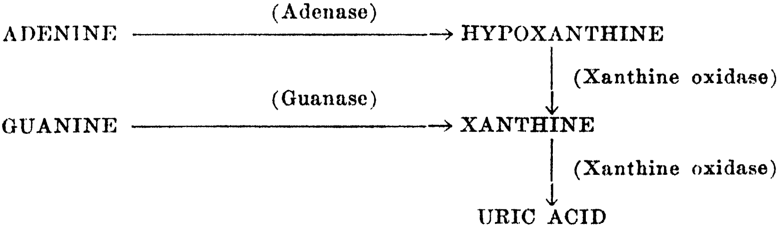
Melanin strongly absorbs both visible and ultraviolet light and its function is to protect the tissues below the skin from radiant energy, particularly from the ultraviolet radiant energy of the sun. As all of us know, exposure to sunlight causes an increase in the melanin content of the skin (that is, causes tanning). Just how this increase is brought about is not known, but it is interesting that dopa is formed when tyrosine in solution is exposed to ultraviolet radiant energy.

There is evidence that small amounts of melanin are eliminated from the body in the urine and stools. Probably larger amounts are lost by desquamation (sloughing off of skin). Of course, loss of melanin also occurs whenever hair is removed from the body.

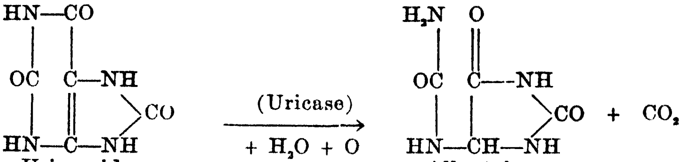
The characteristic color of red hair appears to be due to the presence of an oxidation product of melanin.

Purine and Pyrimidine Metabolism.—Purines and pyrimidines occur in nearly every cell in the body, since they are constituents of nucleoproteins. We have good evidence that the body can manufacture these substances, even if they are absent from the diet. For example, a growing infant builds thousands of new cells every day, although the milk that makes up most, or all, of his diet does not contain purines or pyrimidines. A newly hatched chick contains much larger quantities of purines and pyrimidines than were present originally in the egg.

The purines present in nucleoprotein molecules are *adenine* and *guanine*. When nucleoprotein is catabolized (broken down), these compounds are converted to uric acid, principally in the liver. Xanthine and hypoxanthine are formed as intermediate compounds. In the following diagram, the enzymes that catalyze the various reactions are indicated by parentheses.



In the case of man and the higher apes the uric acid formed by purine catabolism is excreted unchanged in the urine. Other higher animals, whose livers contain an enzyme known as *uricase,* convert the uric acid to *allantoin,* which is then eliminated in the urine as an end product of metabolism.



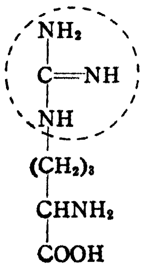
Uric acid Allantoin

Dalmatian coach hounds excrete both uric acid and allantoin. It will be recalled that birds and reptiles convert ammonia, as well as purines, to uric acid, which then is eliminated in the excreta. Certain lower animals, such as the frog and the dogfish, convert purines to urea; this substance thus becomes the end product of purine metabolism in these species.

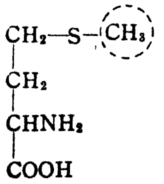
Very little is known about pyrimidine catabolism. There is some evidence that the end product of pyrimidine metabolism is urea.

Creatine and Creatinine.—*Creatine* is found in many tissues of the body. It is present in highest concentration in muscle, where it exists both as free creatine and as creatine phosphate. As we have learned (see page 615), the reversible change of creatine phosphate to creatine and phosphoric acid occurs when muscles contract.

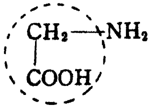
Creatine (methylguanidine-acetic acid) is formed in the body from the three amino acids, arginine, glycine, and methionine. The portion of its molecule donated by each of these acids is indicated in the following formulas by the dotted lines.



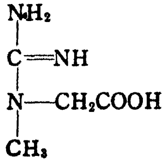
Arginine



Methionine

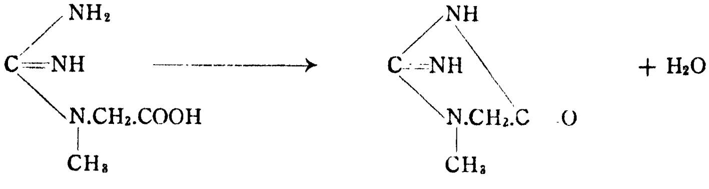


Glycine



Creatine

Creatine is changed in the body to *creatinine,* which then is excreted in the urine.

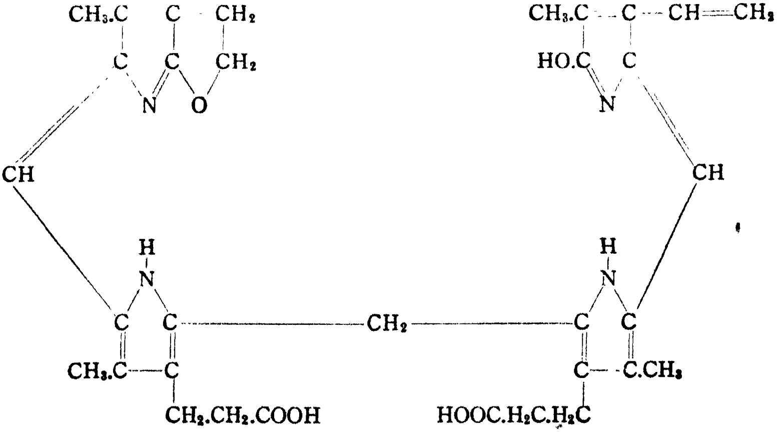


Creatine

Creatinine

Creatine, as well as creatinine, occurs in the urine during childhood, but usually is present only in small amounts in normal samples of the urine of adults.

Hemoglobin Metabolism.—Hemoglobin is manufactured in the bone marrow (soft inner portion of bones). Iron and amino acids are necessary for its synthesis (see page 590). Copper is not a part of the molecule, but it acts as a catalyst for the synthetic reaction, and hemoglobin formation cannot take place at a normal rate unless this metal is in the diet. We do not know with certainty what material is used for the synthesis of the porphyrin ring system of heme, although there is good evidence



Bilirubin
(Compare with formula for heme on page 590.)

that the nitrogen, and perhaps some of the carbons also, of this ring are derived from the amino acid, glycine.

The catabolism of hemoglobin takes place in the liver, spleen, and bone marrow. The first breakdown product formed appears to be *verdohemochromogen.* This substance resembles hemoglobin, but it has a greenish color. Verdohemochromogen then loses iron and protein to form *biliverdin.* Biliverdin next is converted to *bilirubin,* the substance responsible for most of the yellow color of plasma.

Bilirubin is removed from the blood stream by the liver. It passes from the liver to the intestinal tract as a component of the bile (see page 629).

In the presence of the intestinal bacteria, bilirubin undergoes several changes. It is first reduced to colorless substances known as *urobilinogen* and *stercobilinogen.* These compounds then are oxidized to the brown pigments, *urobilin* and *stercobilin,* which are responsible for most of the normal color of the stools.

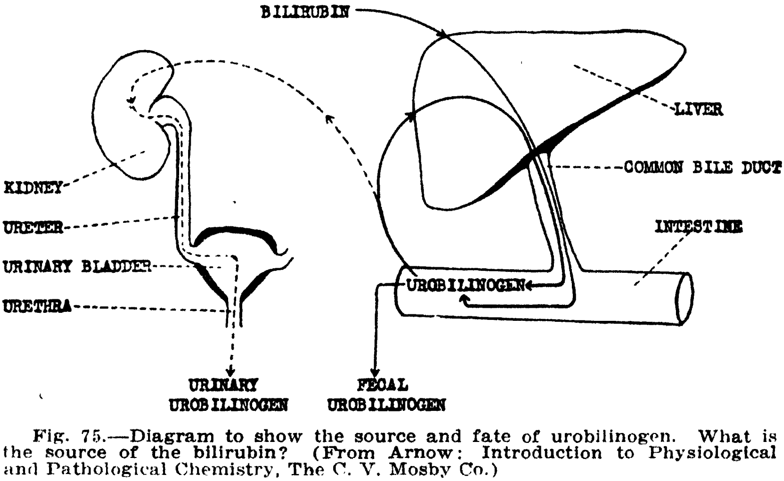


Fig. 75.—Diagram to show the source and fate of urobilinogen. What is the source of the bilirubin? (From Arnow: Introduction to Physiological and Pathological Chemistry, The C. V. Mosby Co.)

A certain amount of the urobilinogen (and stercobilinogen) diffuses from the intestine into the blood. However, as the blood leaving the intestine passes through the liver, most of the urobilinogen present in it is removed. The fate of this urobilinogen is not known with certainty, but it is thought that a portion of it enters the intestine again with the bile. Small amounts of the urobilinogen absorbed from the intestine succeed in passing through the liver without being removed from the blood, and are excreted in the urine. The amount present in a twenty-four-hour sample of urine ordinarily is less than 3 mg.

Excretion

Most of the organic substances present in urine are end products of amino acid or conjugated protein catabolism. They include:

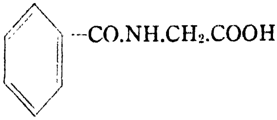
(1) *Urea.* This substance is formed in the liver from the ammonia produced by the oxidative deamination of amino acids. Perhaps some of it is derived from pyrimidine catabolism.

(2) *Uric acid and allantoin.* These compounds are end products of purine metabolism. Allantoin is not present in the urine of man or the higher apes. Most other higher animals excrete allantoin, but not uric acid.

(3) *Creatinine. Creatine,* the substance from which creatinine is made in the body, also occurs in the urine in childhood, but ordinarily is present only in small amounts during adult life.

(4) *Urochrome.* This substance is responsible for most of the color of normal urine. It contains nitrogen and, therefore, must be a product of protein metabolism. Its structure has not been established.

(5) *Hippuric acid.* This compound is formed both in the liver and in the kidney tubules. On hydrolysis it yields benzoic acid and glycine. It is supposed that the body renders benzoic acid (present in many foods) less toxic by converting it to hippuric acid.



Hippuric acid

Ammonium salts are formed by the kidney tubules, probably chiefly from glutamine, the amide of the amino acid, glutamic acid. The content of ammonium salt is correlated roughly with the acidity of the urine; that is, the more acid the urine, the higher the content of ammonium salt. Probably the actual ammonium compound formed by the kidney is ammonium bicarbonate.

$$\underset{\text{Ammonia}}{NH_3} + \underset{\text{Water}}{H_2O} + \underset{\text{Carbon dioxide}}{CO_2} \rightarrow \underset{\substack{\text{Ammonium}\\ \text{bicarbonate}}}{NH_4HCO_3}$$

This substance then combines with the sodium salts of acids. For example, during ketosis, acetoacetic acid is excreted partly as its sodium salt. In the presence of ammonium bicarbonate, sodium bicarbonate and ammonium acetoacetate are formed.

$$\underset{\substack{\text{Sodium}\\ \text{acetoacetate}}}{CH_3.CO.CH_2.COONa} + \underset{\substack{\text{Ammonium}\\ \text{bicarbonate}}}{NH_4HCO_3} \rightarrow \underset{\substack{\text{Sodium}\\ \text{bicarbonate}}}{NaHCO_3} + \underset{\substack{\text{Ammonium}\\ \text{acetoacetate}}}{CH_3.CO.CH_2.COONH_4}$$

The sodium bicarbonate formed in this reaction diffuses back into the blood and the ammonium acetoacetate is excreted. The importance of the formation of ammonium salts by the kidney lies in the fact that it helps prevent an excessive loss of base (sodium bicarbonate) from the body when acids are eliminated in the urine.

The phosphates and sulfates present in urine are end products of the metabolism of phosphoproteins and the sulfur-containing amino acids.

The carbon dioxide and water formed when amino acid residues are oxidized in the body are eliminated as described in Chapter XXIII.

Study Questions

1. Is saliva an important digestive fluid for proteins?
2. What is the approximate pH of freshly secreted gastric juice?
3. Does the gastric juice of all normal adults contain HCl?
4. Why does the pH of the stomach contents rise when food is eaten?
5. What are the functions of the HCl of gastric juice?
6. What is the function of pepsin?
7. Is rennin present in human gastric juice?
8. What is pepsinogen? How is it converted to pepsin?
9. What is the optimum pH for pepsin? What type of compound is this enzyme?
10. How are trypsinogen and chymotrypsinogen converted to active enzymes?

11. What substances are digested by trypsin and chymotrypsin? What are the end products of this digestion?
12. How do carbopeptidases differ from aminopeptidases? Which type is present in pancreatic juice? In intestinal juice?
13. What is the function of dipeptidases?
14. What are the end products of the digestion of simple proteins?
15. List the enzymes concerned in the digestion of nucleic acid and give the functions of each.
16. What is meant by intestinal putrefaction?
17. What compounds are responsible for the odor of the stools? For the color of the stools?
18. List several substances formed by intestinal bacteria from protein, and indicate the amino acid from which each is made.
19. How is indole detoxified in the liver?
20. Describe how amino acids are absorbed from the intestinal tract.
21. How much amino acid nitrogen is present in 100 cc. of blood from a fasting person? Where did these amino acids come from? What happens to them?
22. List several anabolic products of amino acids.
23. Name several antiketogenic and several ketogenic amino acids.
24. Write equations illustrating the oxidative deamination of an amino acid in the liver.
25. What is the fate of the keto acids formed in the liver?
26. What is the fate of the ammonia formed in the liver? What organ manufactures urea?
27. Describe two theories of the mechanism by means of which urea is formed. Illustrate with equations.
28. What is the fate of urea?
29. What substance is secreted by birds and reptiles as an end product of ammonia metabolism?
30. What is meant by transamination? Illustrate by means of an example not given in the book. What enzymes catalyze transaminations?
31. What portion of the protein molecule cannot be oxidized in the body?
32. How many large calories of energy are produced by the complete oxidation of 1 g. of protein in the body?
33. Name the plasma proteins. Which one of them is present in highest concentration in plasma?
34. What tissues are believed to manufacture plasma proteins?
35. Explain how plasma proteins assist in the transfer of food molecules from the blood to the cells, and in the passage of waste products from the cells to the blood.
36. What are antibodies? In what fraction of the plasma protein are they located?
37. List the reactions that occur when blood clots.
38. What vitamin is necessary for the manufacture of prothrombin?

39. What is the suggested function of heparin?
40. What amino acid is thought to be necessary for the formation of melanin?
41. What is dopa? What enzyme catalyzes its conversion to melanin? Where in the body is this enzyme located?
42. List some of the important properties of melanin.
43. What is the function of melanin?
44. How is melanin excreted from the body?
45. Why do we think that purines and pyrimidines can be made in the body?
46. What is the fate of adenine and guanine in the body?
47. What is the end product of purine metabolism in man? In most other higher animals? What is uricase?
48. What animals convert purines to urea?
49. What is thought to be the end product of pyrimidine metabolism?
50. In what type of tissue is creatine found in greatest abundance? What is its function in muscle contraction?
51. What amino acids are required for creatine synthesis? What portion of the creatine molecule is donated by each of these?
52. What type of chemical change occurs when creatine is converted to creatinine?
53. What is the end product of creatine metabolism in the adult?
54. Does creatine normally occur in the urine of children? Of adults?
55. What substances are known to be necessary for hemoglobin synthesis?
56. What is the role of copper in hemoglobin synthesis?
57. In what tissues does hemoglobin breakdown occur?
58. List the various compounds formed during hemoglobin catabolism. What do you suppose is the fate of the protein portion of the hemoglobin molecule?
59. What is the fate of the urobilinogen absorbed from the intestine?
60. How much urobilinogen is present in a twenty-four-hour sample of normal urine?
61. List the more important organic compounds found in urine. From what food substances are they derived?
62. Of what importance is the formation of ammonium salts by the kidney? Explain.
63. What is the source of the phosphates and sulfates in urine?
64. How are the carbon dioxide and water formed during protein metabolism eliminated from the body?

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CHAPTER XXVII

INORGANIC METABOLISM

Water.—Water is the most abundant compound in the body. An infant is approximately 70 per cent water, and the bodies of adults contain from 58 to 65 per cent of this substance. As these average figures indicate, the water content of tissues gradually decreases with aging.

Sources of body water. The daily water intake is correlated in a rough way with the energy output of the body, and averages 1 cc. for each large calorie of energy expended. For most adults who do office or professional work, the amount of water taken into the body each day in the form of drink or moist food will be in the neighborhood of 2,500 cc. Of course, the water requirement is increased greatly by strenuous exercise or by excessively high temperatures. As a rule, two-thirds of the dietary water is derived from the solid and semisolid food ingested; the other one-third must be swallowed in liquid form.

It will be recalled that water is one of the end products of catabolism. In other words, a certain amount of it is produced in the tissues by chemical reactions. The amount gained in this way averages 12 to 14 cc. for each 100 large calories of energy liberated.

Functions of body water. Most of the substances present in the body are dissolved in water, and the great majority of the metabolic chemical reactions could not take place in its absence. Foods are transported to the cells, and waste products to the organs of excretion, by the water of the blood and tissues. The water of the blood stream also distributes heat quickly and uniformly to all parts of the body, and, when the production of heat is excessive, the body is cooled by the evaporation of water from the skin and lungs. Water has a higher surface tension than the other substances present in the body. Since surface active substances tend to collect at interfaces between water and other materials of lower surface tension (see Chapter II), the surface active enzymes of the body collect at the boundary between the water in which they are dissolved and the food to be digested or oxidized. Reactions involving ions could not occur in the absence of water, for, as a rule, ionization does not take place in other solvents.

Table XV indicates the amounts of water used in metabolizing some common foods. This water is used chiefly for the dissipation of the heat of metabolism and for the excretion of waste products. Whenever the protein or inorganic content of the diet is increased, the water requirement increases also.

TABLE XV

GRAMS OF WATER REQUIRED TO METABOLIZE 100 GRAMS OF FOOD

FOOD	GRAMS OF WATER
Protein	350
Starch	46
Fat	48
Beef, sirloin	143
Eggs	156
Milk	43
Bread	102

Distribution of body water. It is convenient to think of water as existing in three regions, or *compartments,* of the body. These compartments are:

(1) *The intracellular compartment.* The water of this compartment is the water present *inside* cells. The protoplasm of which cells are made is about 80 per cent water, and only a small fraction of this can be lost without death of the cells. The intracellular compartment contains 70 to 75 per cent of the total body water.

(2) *The vascular compartment.* The vascular compartment is the blood, which contains about 7 per cent of the body water. Plasma is 91 per cent water; the blood cells are 60 per cent water.

(3) *The interstitial compartment.* Water present in the tissues, but outside the cells, is said to be in this compartment. This water (20 to 25 per cent of the total) serves as a medium for the transport of materials between the cells and the blood. It serves also as *stored water;* that is, during periods of water deprivation, the water necessary for metabolism comes

from it. If the fluid in the interstitial compartment is used up, life no longer is possible. In other words, a loss of from one-fifth to one-fourth of the body water results in death.

Excretion of body water. Water is lost from the body in the urine, in the expired air, and from the skin. Small amounts are lost in the stools and in saliva. Healthy adults excrete each day approximately as much water as they ingest. At rest, approximately 60 per cent is lost in the urine; 20 per cent, from the skin; 14 per cent, in the expired air; and 6 per cent, in the stools. Visible sweating does not occur until the skin temperature exceeds 30° C. (86° F.), but even at lower temperatures water evaporates continuously from the skin ("insensible perspiration"). Insensible perspiration and breathing together cause a loss of about 50 g. body weight per hour. This is explained by the fact that the water and carbon dioxide lost from the body weigh more than the oxygen gained.

Calcium.—*Absorption.* Calcium is present in foods in both organic and inorganic form. There is some evidence, however, that most of it is changed to inorganic form in the intestine prior to absorption. The calcium present in various foods is not equally well absorbed. For example, the calcium of milk readily passes out of the small intestine into the blood, but much of the calcium in vegetable foods is present in insoluble form (for instance, as calcium oxalate) and passes through the digestive tract without absorption.

Calcium absorption is poor when the contents of the intestinal tract are alkaline, because most calcium salts are insoluble in alkaline solution. This is particularly true if the diet contains an excess of fat, since insoluble calcium soaps may be formed. If the diet is high in phosphate, insoluble calcium phosphate may precipitate. Sugars appear to favor calcium absorption, perhaps because small amounts of organic acids are made from them by intestinal bacteria. If the diet of children is deficient in vitamin D (see page 728), calcium absorption is diminished.

Distribution.—Calcium is responsible for about 2 per cent of the body weight. Ninety-seven to 99 per cent of it is located in the bones and teeth. Calcium is not present in red blood cells, but plasma contains 9 to 11.5 mg. per 100 cc. About half of this plasma calcium is in ionic form; the remainder is bound by the plasma proteins. Small amounts of calcium (8 mg. per 100 g.) occur in muscle tissue.

The level of plasma calcium is controlled by the parathyroid glands (see page 690).

Functions of calcium. Among the important functions of calcium are the following:

(1) It is required for the formation of bones and teeth.

(2) It is essential for the clotting of blood.

(3) It is necessary for the maintenance of a normal heart rhythm.

(4) It is a normal component of milk, and is required for milk formation.

(5) Calcium ions tend to depress the irritability of nerves. If the calcium ion level of the blood is too low, nerves are over-irritable, and tetany (a condition characterized by convulsions, or spasmodic contractions of muscles) results. When the calcium ion level of the plasma is too high, nerves are depressed and coma (a state of unconsciousness resembling anesthesia) may result.

(6) Calcium is essential for a normal rate of growth of young animals.

Excretion. Calcium leaves the body in the stools and in the urine. The amount present in the stools (0.4 to 0.8 g. per day) makes up about two-thirds of the total excreted. Undoubtedly, much of this represents material that was not absorbed, but some of it probably enters the intestine with the digestive secretions. Any factor that increases calcium absorption also increases the percentage of the element excreted in the urine.

Phosphorus.—*Absorption.* Approximately two-thirds of the phosphorus present in average normal diets is absorbed from the intestinal tract. Most of the food phosphorus is present in nucleoproteins, phosphoproteins, and phospholipids. Excessive amounts of calcium in the diet inhibit phosphate absorption. Vitamin D is necessary for optimal absorption during childhood.

Distribution. Most of the phosphorus of the body is in the bones and teeth. However, small amounts are present in all nucleated cells, since phosphoric acid is a constituent of nucleoproteins. The total phosphorus of plasma varies from 8 to 18 mg. per 100 cc. Red blood cells contain from 47 mg. to 114 mg. in each 100 cc. Most of the blood phosphorus is present in organic form. Blood plasma contains from 2.5 to 4.5 mg. of inorganic, acid-soluble phosphorus per 100 cc. Red blood cells contain slightly lower amounts.

Functions of phosphorus. (1) Phosphorus is required for the synthesis of bones and teeth.

(2) It is necessary for the formation of nucleoprotein, phospholipids, sugar esters, and other organic phosphorus compounds in the tissues.

(3) Phosphate salts act as buffers in blood and urine.

(4) Phosphoric acid and organic phosphorus compounds are necessary for normal muscle contraction (see page 616).

(5) It is necessary for the formation of milk. Casein, one of the principal milk proteins, is a phosphoprotein.

(6) It may be necessary for the absorption of sugars from the intestinal tract and from the kidney tubules (see pages 607 and 624).

(7) It is required for normal growth of young animals.

Excretion. About two-thirds of the phosphorus eliminated from the body is excreted in the urine. The remainder is present in the stools. The phosphorus present in urine is largely a mixture of monosodium phosphate and disodium phosphate. Blood plasma, which is slightly alkaline, contains four times as much disodium phosphate as monosodium phosphate. In the kidney tubules some of this disodium phosphate is converted to the monosodium salt.

$$\underset{\substack{\text{Disodium}\\ \text{phosphate}}}{Na_2HPO_4} + \underset{\substack{\text{Carbonic}\\ \text{acid}}}{H_2CO_3} \rightarrow \underset{\substack{\text{Monosodium}\\ \text{phosphate}}}{NaH_2PO_4} + \underset{\substack{\text{Sodium}\\ \text{bicarbonate}}}{NaHCO_3}$$

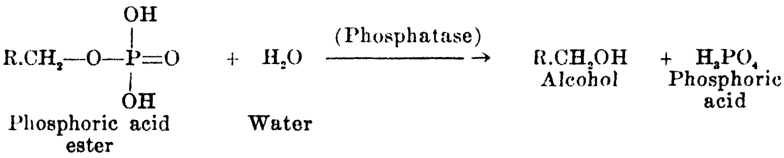
The sodium bicarbonate formed by this reaction diffuses back into the blood. In an average sample of urine, the ratio of NaH_2PO_4 to Na_2HPO_4 is about 9:1, and the pH is in the neighborhood of 6.

The Calcification Process.—The inorganic phase of calcified tissues (bones and teeth) is similar in chemical composition to the group of minerals known as the *apatites.* The empirical formulas of some of these apatites are given below:

$CaF_2[Ca_3(PO_4)_2]_3$	$CaCl_2[Ca_3(PO_4)_2]_3$	$CaCO_3[Ca_3(PO_4)_2]_3$
Fluorapatite	Chlorapatite	Dahllite

Small amounts of magnesium, sodium, and potassium also are present, both in the minerals and in bones and teeth. Some scientists have suggested that the inorganic phase of calcified tissues should be regarded as a crystalline mass in which the various atoms and radicals are grouped in a definite geometric fashion. In certain regions of the crystalline mass some of the oxygen atoms may be replaced by OH or F groups; in other regions, some of the fluorine atoms may be replaced by OH, Cl, or O; some positions ordinarily occupied by phosphorus may be occupied in certain regions by carbon; and some of the calcium positions may be filled by carbon atoms. The small percentages of magnesium, sodium, and potassium present in bones and teeth can be explained by assuming that these elements have substituted for calcium.

An enzyme, known as *phosphatase,* is present in high concentration in bone. This enzyme is believed to catalyze the hydrolysis of phosphoric acid esters in the region of the bone, thus causing an increase in the concentration of phosphate ions in this region.



$$R.CH_2{-}O{-}\overset{\overset{\textstyle OH}{|}}{\underset{\underset{\textstyle OH}{|}}{P}}{=}O + H_2O \xrightarrow{\text{(Phosphatase)}} R.CH_2OH + H_3PO_4$$

In the presence of the calcium ions of the tissue fluids, a precipitate forms in the bone. This precipitate is thought to be either $CaHPO_4$ or a mixture of $CaHPO_4$ and $Ca_3(PO_4)_2$. As time goes on, the $CaHPO_4$ changes to $Ca_3(PO_4)_2$. Calcium and carbonate ions then are deposited in equivalent amounts. These events cause the formation of the crystalline bone mass. Various exchanges gradually take place, leading to the introduction of F, OH, Mg, K, and Na, as suggested above.

Iron.—The body of a normal adult contains about 4 g. of iron, and three-fourths of this is present in hemoglobin. Most of the other one-fourth is stored in the liver; smaller amounts are stored in the spleen, kidneys, and muscles; and some iron is present in the molecules of certain of the respiratory enzymes (see Chapter XXIII).

The absorption of iron from the intestinal tract is increased by the presence of acids, bile, and calcium; it is inhibited by alkalies. It seems to be true that the absorption of iron is increased whenever the need for this element is great. Certain organic forms of iron, such as heme iron, cannot readily be absorbed. There is evidence that ferrous iron (valence 2+) is more readily absorbed than ferric iron (valence 3+); indeed, some scientists believe that trivalent iron always is converted to divalent form in the intestine prior to absorption.

Plasma contains only very small amounts of iron (0.1 to 0.13 mg. per 100 cc.). This plasma iron has a valence of 3+. Most of the blood iron is present in the red blood cells. About 90 to 95 per cent of the red cell iron is combined with hemoglobin. The remaining 5 to 10 per cent is called "easily split off iron," because it is changed to inorganic form by the addition of mineral acids. Perhaps the "easily split off iron" is present as verdohemochromogen (see page 658).

Only traces of iron are lost from the body each day, unless bleeding occurs. The iron released during the catabolism of hemoglobin appears to be stored for a time in the liver, or in other organs, after which it takes part in the formation of new hemoglobin.

Ferritin. Many tissues of the body, and particularly the liver, spleen, and intestinal mucosa, contain a colorless protein known as apoferritin. Under physiologic conditions, apoferritin combines with iron (probably as $Fe(OH)_2$) to form a conjugated protein known as *ferritin*. Crystalline ferritin contains approximately 23 per cent of iron, all in the ferric state. There is increasing evidence that much, if not all, of the stored iron of the body (i.e., iron not present in active molecules such as hemoglobin and tissue enzymes) is present as ferritin. It has been suggested that ferritin plays an important role in the absorption of iron from the intestinal tract. According to this theory, iron is absorbed into the cells lining the small intestine in ferrous form. In the intestinal mucosal cells, the ferrous iron combines with apoferritin to form ferritin, and thus becomes Fe^{+++}. After a time, all the apoferritin present will have been converted to ferritin, and the cells will be "physiologically saturated" with Fe^{++}. Under these conditions, further absorption of iron from the intestinal tract ceases. Now, it is assumed also that the Fe^{++} present in the cells is in equilibrium with the Fe^{+++} present in the plasma. (It will be recalled that the iron of the plasma has a valence of 3^{+}.) Whenever the body requires more iron, the level of plasma iron falls, and some of the Fe^{++} present in the intestinal cells is converted to plasma iron. Under these circumstances, some of the ferritin dissociates to form apoferritin and Fe^{++}. When the amount of ferritin becomes low, more iron then will be absorbed from the intestinal tract, and the content of ferritin will increase again. This theory appears to explain the puzzling observation that iron is not readily absorbed from the intestine except when the physiologic need for it is great (i.e., when the body stores of iron are lowered by loss of blood or by disease).

Copper and Cobalt.—Copper is not a part of the hemoglobin molecule, but it appears to be necessary as a catalyst for hemoglobin synthesis. If it is absent from the diet, anemia (lowered blood level of hemoglobin and red blood cells) results. Some copper is stored in the liver, and blood contains traces of it.

Certain animals (for example, cattle) appear to need cobalt also for normal metabolism. Cobalt is apparently a catalyst for hemoglobin formation, for an anemia develops if it is absent from the diet.

Iodine.—Iodine is necessary for the formation of *thyroxine,* the hormone of the thyroid gland (see page 687). Indeed, this substance is 65 per cent iodine by weight. Of the 25 mg. of iodine present in the average adult body, 15 mg. (60 per cent) are located in the thyroid gland. Blood contains about 0.005 to 0.014 mg. of iodine per 100 cc. There is evidence that something like half of the total blood iodine is present in the form of thyroid hormone.

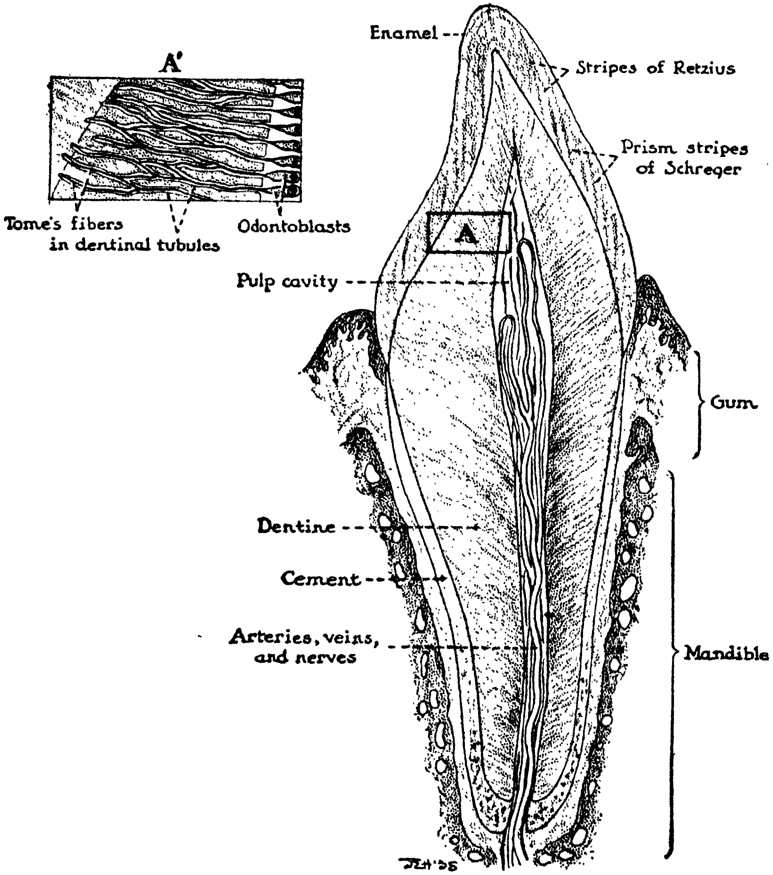

A'
Tome's fibers in dentinal tubules
Odontoblasts
Enamel
Stripes of Retzius
Prism stripes of Schreger
A
Pulp cavity
Gum
Dentine
Cement
Arteries, veins, and nerves
Mandible

Fig. 76.—Longitudinal section of an incisor tooth. How does the fluorine content of the enamel of decayed teeth compare with that of the enamel of normal teeth? (From McClendon and Pettibone: Physiological Chemistry.)

Fluorine.—Most of the fluorine of the body is present in the bones and teeth (see page 669). The highest concentration of it is found in the enamel (outer portion) of the teeth. If the water drunk during the first seven years of life (the period during which the enamel of the permanent teeth develops) contains high amounts of fluorine, a condition known as *mottled enamel* results. The enamel of mottled teeth has a chalky appearance, and readily adsorbs stains from the food. This type of enamel is harder than normal, but is more brittle.

It is now well established that the fluorine of the enamel protects in some way against the development of dental caries (tooth decay). In regions where the drinking water is fairly high in fluorine, the incidence of tooth decay is low. In other regions, where only traces of fluorine are present in the surface water, dental decay is extremely common. Moreover, it can be shown by chemical analysis that the remaining enamel of decayed teeth contains less fluorine than the enamel of sound teeth.

The immediate cause of dental caries is thought to be the erosion (solution) of enamel by organic acids. These acids are formed from the carbohydrate of the food by certain strains of bacteria present in the mouths of persons susceptible to dental decay. Strangely enough, these bacteria are not present ordinarily in the mouths of people whose teeth are not carious (decayed). Just how the presence of high amounts of fluorine in enamel can have an influence on the growth of these bacteria, or on the production of acids by them, is not known at the present time.

Sodium Chloride.—An average adult eats from 5 to 15 g. of sodium chloride each day, and excretes about this same amount in the urine. During a fast the amount eliminated in the urine falls to very low levels; that is, the body conserves salt when it is not present in the diet.

Sweat contains sodium chloride (approximately 0.7 per cent when sweating is profuse), and excessive sweating may result in the loss of relatively large amounts of salt. If too much is lost in this way, the osmotic pressure of the fluid of the extracellular compartment of the body becomes lower than is usual. This causes water to pass into the body cells, which then become more irritable than normal. Headache, muscular tremors, convulsions, vomiting, diarrhea, and prostration may appear. This condition is known as *miners' cramps* or *stokers' cramps.* The loss of sodium chloride as a result of profuse sweating is a common cause of one type of "heat stroke."

The ingestion of excessive amounts of sodium chloride leads to an increase in the amount of fluid stored in the interstitial compartment of the body. Under ordinary circumstances this does no harm, but in certain pathological conditions amazingly large quantities of water may be stored in this compartment unless the sodium chloride intake is lowered.

Chloride ions can pass across the membrane of red blood cells in both directions; that is, chloride ions are present both inside these cells and in the plasma. However, the other body cells apparently do not contain chloride ions. It is interesting, too, that most of the sodium ions of the body are outside cells.

Sodium Bicarbonate.—Sodium bicarbonate is the chief alkaline buffer of the blood. It makes up most of the so-called *alkali reserve* of the blood. This compound protects against large changes in pH when acids enter the blood. Suppose, for example, that some 0.1 N hydrochloric acid is injected into the blood stream of an animal. It will be neutralized immediately by sodium bicarbonate.

$$\underset{\substack{\text{Hydrochloric}\\ \text{acid}}}{HCl} + \underset{\substack{\text{Sodium}\\ \text{bicarbonate}}}{NaHCO_3} \rightarrow \underset{\substack{\text{Sodium}\\ \text{chloride}}}{NaCl} + \underset{\substack{\text{Carbonic}\\ \text{acid}}}{H_2CO_3}$$

The carbonic acid quickly decomposes to form carbon dioxide and water. These reactions cause a slight lowering of the sodium bicarbonate and a slight elevation of the sodium chloride levels of the blood, but the pH does not change appreciably.

We have learned that carbon dioxide is transported from the tissues to the lungs largely in the form of sodium bicarbonate (Chapter XXIII).

Potassium.—Most of the potassium ions of the body are present *inside* cells. It will be recalled that sodium ions are, for the most part, found in the fluids outside the cells.

The potassium excreted in the urine each day (about 2 g.) is equal on the average to the potassium intake.

Potassium is necessary for the proper relaxation of the heart between beats. It is present in high concentration in nerve tissue, and is probably of great importance for the conduction of nerve impulses.

Sulfur.—Nearly all the sulfur present in a normal diet is found in the sulfur-containing amino acids (methionine, cystine, cysteine) of the food proteins. Some of the substances in the tissues that contain sulfur are:

(1) Proteins.

(2) Glutathione. This is a tripeptide, composed of glycine, cysteine, and glutamic acid. It is found in nearly all tissues. Since the —SH group of the cysteine easily is oxidized to the —S—S— group, it is supposed that the tripeptide may be important in some of the tissue oxidations and reductions. There is some evidence indicating that glutathione is particularly important for some phases of protein metabolism.

(3) Taurine, which is present in taurocholic acid and its salts (see page 635).

(4) Insulin, the hormone of the isles of Langerhans. This substance is a protein.

Keratin, the scleroprotein of the skin and hair, contains relatively large amounts of cystine, and sulfur is lost from the body whenever hair or skin is lost. Small amounts of sulfur-containing compounds enter the intestinal tract with the bile, and are excreted with the stools. Approximately 0.9 g. of sulfur is eliminated each day in the urine. Most (80 per cent) of the urinary sulfur is in the form of inorganic sulfates.

Study Questions

1. What percentage of the adult body is water?
2. In what direction does the water content of tissues change with aging?
3. List the sources of body water.
4. Approximately how many cubic centimeters of water will be required per day by a person whose daily energy requirement is 3,000 large calories?
5. On the average, what percentage of the daily water intake must be drunk?

6. How much water is produced in the body for each 1,000 large calories of energy expended?
7. List the major functions of body water.
8. Which one of the following would require most water per unit weight for its complete metabolism in the body: potatoes, beef, egg albumin, sugar, milk? Explain.
9. What are the three compartments in which the body water may be assumed to exist? What fraction of the total water of the body normally is present in each? Which compartment contains stored water?
10. What percentage of body water can be lost before death occurs?
11. How is water excreted from the body? What percentage is excreted by each route?
12. Explain why insensible perspiration and breathing cause a loss of weight.
13. What factors inhibit calcium absorption? What factors assist it?
14. What fraction of the body calcium is located in the bones and teeth?
15. How much calcium is present in 100 cc. of blood plasma? What fraction of this calcium is in ionic form?
16. Do red blood cells contain calcium?
17. What endocrine gland controls the level of blood calcium?
18. List 6 functions of calcium in the body.
19. Under normal circumstances, what percentage of calcium excretion occurs by way of the intestinal tract?
20. What substances in food contain most of the dietary phosphorus?
21. Why do excessive amounts of calcium inhibit phosphorus absorption?
22. Discuss the distribution of phosphorus in the body.
23. List 7 functions of phosphorus in the body.
24. What fraction of the phosphorus lost from the body each day is excreted in the urine?
25. What reaction in the kidney tubules assists in lowering the pH of urine below that of blood plasma?
26. Discuss briefly the composition of bones and teeth, and describe the calcification process.
27. What is the supposed function of bone phosphatase?
28. How much iron is present in the average adult body? What fraction of this iron is combined in hemoglobin?
29. In what tissues is iron stored? What is ferritin?
30. What factors favor the absorption of iron? What factors inhibit it?
31. What three forms of iron are found in blood? (Plasma iron is inorganic.) Which form is present in greatest abundance?
32. Is the daily loss of body iron very high?
33. What is the function of copper? Of cobalt?
34. Why is iodine necessary in the diet?
35. How much iodine is present in the body? How much of this is in the thyroid gland?

36. How much iodine is present in blood? What fraction of this is thought to be hormone iodine?
37. What condition is caused by an excessive intake of fluorine during early childhood?
38. What part does fluorine play in the prevention of dental decay?
39. What is thought to be the immediate cause of dental caries?
40. How much sodium chloride is eaten each day by an average person? How much is excreted each day?
41. How is the excretion of sodium chloride altered by a fast?
42. What is the cause of stokers' cramps?
43. How does sodium chloride ingestion affect the amount of water in the interstitial compartment?
44. What is peculiar about the distribution of chloride ions, sodium ions, and potassium ions in the body?
45. What substance is responsible for most of the alkali reserve of the blood?
46. How much potassium is excreted in the urine each day? How much is eaten each day?
47. List two functions of potassium.
48. What compounds contain most of the dietary sulfur?
49. List some substances in the tissues that contain sulfur.
50. What is thought to be the function of glutathione?
51. How much sulfur is excreted each day in the urine? How much of this is in inorganic form?
52. By what other routes is sulfur lost from the body?

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CHAPTER XXVIII

HORMONES

Introduction.—The term *hormone* is derived from a Greek word meaning "to stimulate." Hormones are manufactured by specialized groups of cells, known as *ductless glands, glands of internal secretion,* or *endocrine glands.* These glands are clusters of cells without ducts; the secretions made by them diffuse directly into the blood. As a rule, hormones do not influence the cells that make them. Instead, they are carried to other regions of the body where they exert their characteristic metabolic effects. Only minute amounts of these substances are required each day for normal metabolism. It is supposed that hormones act as catalysts for many of the chemical reactions that take place in the body.

Hormones of the Pancreas.—*Insulin.* Insulin is the name given to the hormone produced by the isles of Langerhans of the pancreas (see page 620). Active solutions of this substance were prepared by Banting and Best, who worked in Macleod's laboratory in Toronto, in 1922. Banting and Macleod later were given the Nobel prize for this achievement. The hormone was obtained in crystalline form by Abel in 1926. It is a protein, and has a molecular weight of about 45,000. The following amino acids have been found to be present in the insulin molecule: tyrosine, 12.3 per cent; cystine, 11.6 per cent; glutamic acid, 20.2 per cent; leucine, 13.4 per cent; arginine, 3.5 per cent; histidine, 5.3 per cent; lysine, 2.6 per cent; proline, 2.9 per cent; phenylalanine, 7.9 per cent; glycine, 4.6 per cent; valine, 8.8 per cent; isoleucine, 2.9 per cent; aspartic acid, 6.8 per cent; serine, 5.8 per cent; and threonine, 3.2 per cent. The —S—S— linkage of the cystine apparently is necessary for activity; when it is treated with reducing agents that change this group to —SH groups, the hormone becomes inactive. Reagents that combine with the —OH group of the tyrosine also cause a loss of physiological activity.

When the pancreas is removed from an animal, or when the isles of Langerhans of human beings become underactive, the disease known as *diabetes mellitus* results. Diabetes means "increased flow of urine," and mellitus means "sweet." This condition is characterized by a rise of the blood sugar level, the appearance of glucose in the urine, a loss of the stored

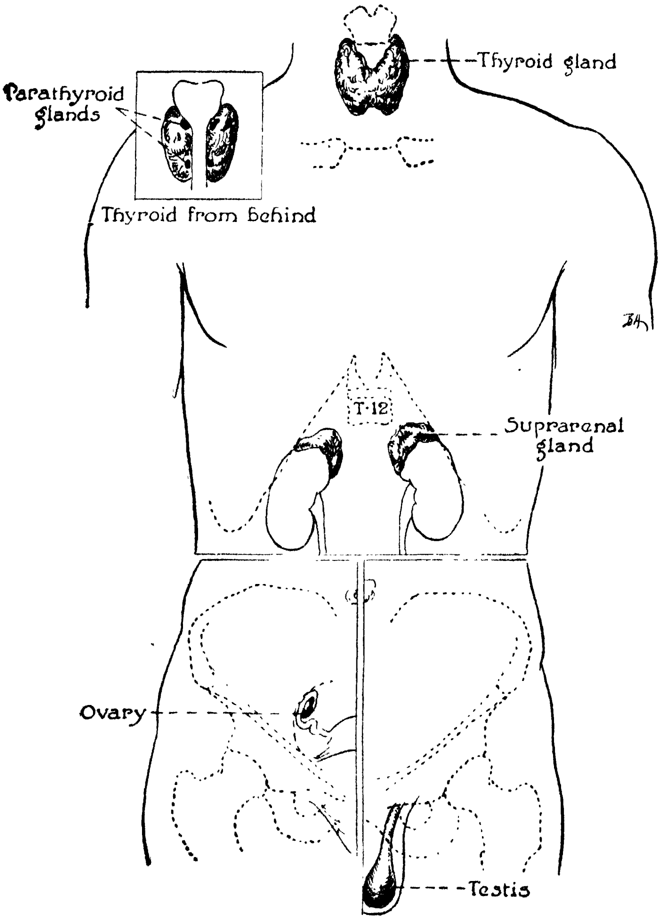


Fig. 77.—Drawing to show the location of some of the endocrine glands. How would you define the term hormone? (From McClendon and Pettibone: Physiological Chemistry, The C. V. Mosby Co.)

glycogen of the body, and ketosis. Hunger, thirst, and an increased elimination of urine also are noticed. All of these abnormal changes can be reversed by the injection of proper amounts of insulin into the animal or human patient. The hormone is not effective if it is given by mouth, since it is digested by the proteolytic enzymes of the intestinal tract.

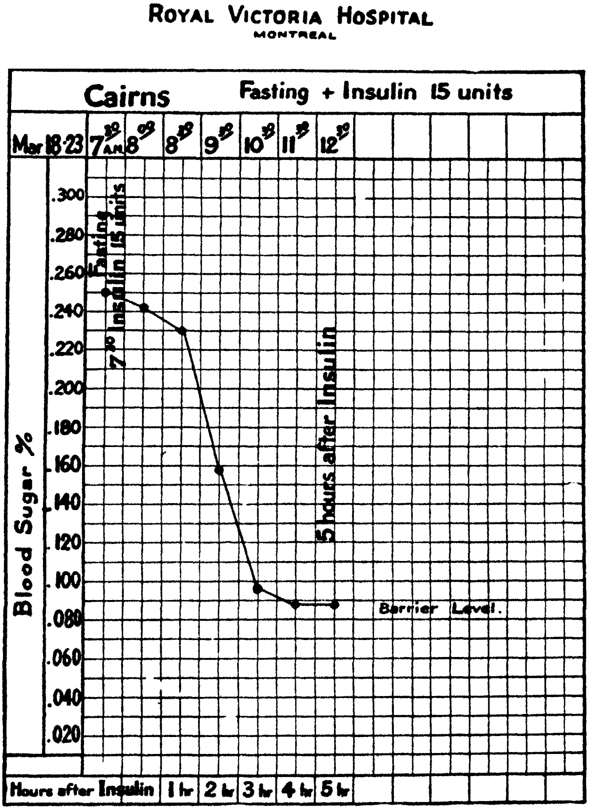


Fig. 78.—Chart showing the effect of an insulin injection on the level of blood sugar. What are the functions of insulin? (From Meakins: The Practice of Medicine, The C. V. Mosby Co.)

It is generally agreed that the injection of insulin into a diabetic animal causes a fall of the level of blood glucose, an increased deposition of muscle glycogen, and a decrease in the rate of production of ketone bodies. Liver glycogen increases also, but there is still uncertainty as to the correct explanation for this. Many biochemists believe that insulin decreases the rate of breakdown of liver glycogen to glucose. Since glycogen formation in the liver is continuous, the decreased glycogenolysis (glycogen breakdown) thought to be caused by insulin would result in an increase in the glycogen stored in this organ. Most biochemists agree that the rate of carbohydrate oxidation increases following an injection of insulin. Evidence that insulin can affect the rate of conversion of glucose-6-phosphate to glycogen has been discussed on page 621.

It will be recalled that liver glycogen breaks down to glucose in the normal animal whenever the blood sugar level is too low. If insulin is injected into normal (nondiabetic) animals or human beings, the blood sugar level falls below normal. Under these circumstances liver glycogenolysis occurs, and the amount of glycogen in the liver decreases. In other words, it appears that an abnormally low blood sugar level is more than able to overcome the inhibiting effect of insulin on liver glycogen breakdown.

Occasionally, adenomas (tumors, or new growths of tissue) composed almost entirely of insulin-producing cells form in the pancreas. These adenomas produce abnormally large amounts of insulin and cause symptoms of overactivity (hyperinsulinism). The person with hyperinsulinism undergoes periods when his blood sugar level falls to dangerously low values. This low blood sugar is accompanied by weakness, apprehension, dizziness, faintness, convulsions (sometimes), and unconsciousness. These same symptoms are produced if a diabetic patient takes an overdose of insulin.

Pancreatic anti-fatty liver principle. It has been found that the livers of diabetic dogs contain increased amounts of lipid (neutral fat, cholesterol, and cholesterol esters), even when adequate amounts of insulin are given. Several groups of investigators have described the preparation of pancreatic extracts that prevent this accumulation of lipid when they are fed or injected. Raw pancreas and pancreatic juice are themselves effective when they are fed to the experimental animals. One extract, known as *lipocaic,* has been the subject of much controversy in the literature. Lipocaic is stated to prevent the type of fatty liver that develops in rats fed diets high in fat and low in protein. This same result can be obtained by feeding methionine or choline (see page 718), and there is some doubt whether lipocaic contains a new lipotropic principle (i.e., principle capable of decreasing liver fat) or whether its activity is due to the presence of known lipotropic agents such as methionine and choline. At least one extract of pancreas known to be active in preventing the appearance of fatty livers in diabetic dogs maintained with insulin has been found not to influence the fatty livers produced in rats by feeding high-fat, low-protein diets.

Hormones of the Adrenal Glands.—The two adrenal (''next to the kidney'') or suprarenal (''above the kidney'') glands are attached to the upper part of the kidneys. Each gland consists of an inner portion, called the *medulla,* and an outer portion, called the *cortex.*

Hormone of the medulla. The hormone produced by the cells of the adrenal medulla is known as *adrenaline,* or *epinephrine.* The medulla can be removed from animals without producing marked symptoms, and this portion of the gland is not essential for life. However, when adrenaline is injected, the following effects are noticed:

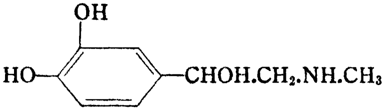
(1) There is an immediate breakdown of liver glycogen and muscle glycogen, with a consequent rise of the levels of blood glucose and lactic acid. After a time, most of the excess glucose and lactic acid are deposited in the liver as glycogen.

(2) Blood pressure rises. This is caused by a constriction of the muscles of the arterioles (small arteries) of the body.

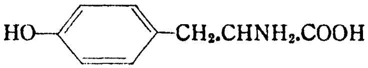
(3) The bronchi (air tubes leading into the lungs) dilate, permitting air to enter the lungs with less exertion on the part of the animal or person. The blood vessels of the mucous membrane (lining) of the nose constrict. This increases the amount of space available for the passage of air through the nasal cavity.

Apparently, adrenaline secretion is stimulated by such emotions as fear or anger. The effects produced by this secretion increase the capacity of the person for ''fight or flight,'' as the case may be.

It is believed that adrenaline is made from the amino acid tyrosine.

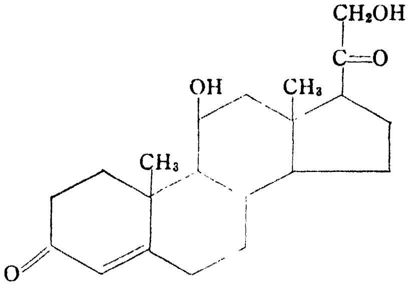


Adrenaline



Tyrosine

Hormones of the cortex. The cortex of the adrenal is necessary for life. It makes several substances necessary for normal metabolism. A solution of these compounds is known as *cortin.* The active substances that have been isolated from cortin are related chemically to cholesterol, the bile salts, vitamin D, and the sex hormones. One of them is known as *corticosterone.*



Corticosterone

The following biochemical abnormalities are produced by the removal of the adrenal cortex:

(1) There are an increased elimination of sodium chloride in the urine, and a decreased level of it in the blood.

(2) There are a decreased elimination of potassium by the kidney, and an increase in the amount of potassium in the blood and tissue fluids.

(3) The glycogen stores in the liver and muscles decrease, and the fasting level of blood glucose is lower than normal.

(4) A certain amount of water leaves the blood stream. Part of this is stored in the tissues; the remainder is eliminated from the body by the kidney.

(5) Some of the end products of metabolism are not excreted properly by the kidney, with the result that the blood level of

nonprotein nitrogen (i. e., the nitrogen in such compounds as urea, uric acid, creatinine, etc.) rises.

(6) The level of plasma globulin rises. When active extracts of the adrenal cortex are injected into animals, one of the effects produced is the breakdown of many of the lymphocytes (one type of "white blood cell") in the blood and in many tissues of the body. This breakdown results in the release of many substances from these cells, including globulins. In some cases these globulins contain antibodies, and, when this is true, the injection of cortical extract causes the level of antibodies in the blood to rise. The finding that the adrenal cortex has as one of its most important functions the regulation of the rate of

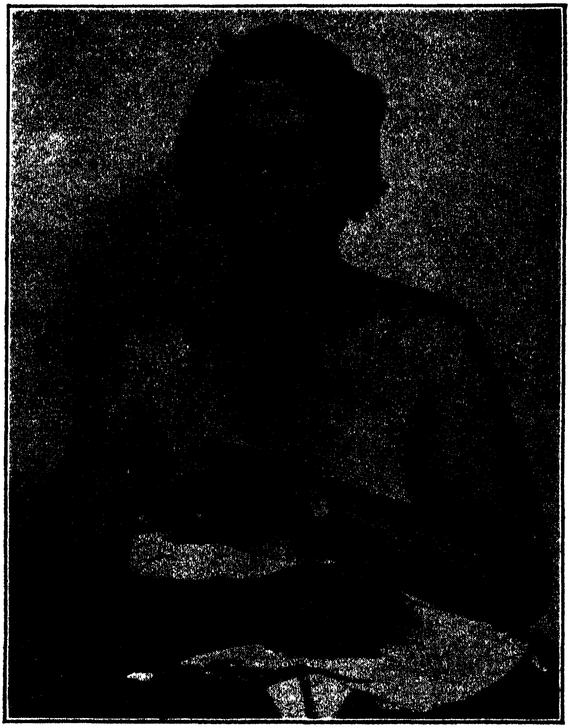


Fig. 79.—Photograph of a patient with Addison's disease. What is the cause of this condition? (From Meakins: The Practice of Medicine, The C. V. Mosby Co.)

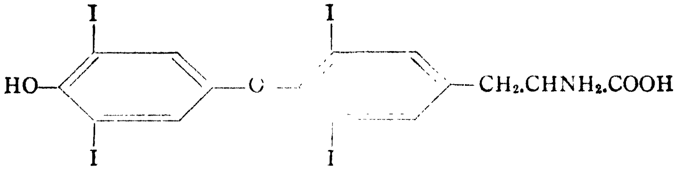
lymphocyte breakdown in the body, and consequently the regulation of the rate of release of the contents of these cells to the various tissues, is one of the most important physiologic discoveries of recent years. It was made by Dr. A. White and Dr. T. F. Dougherty, working at Yale University.

Animals from which the adrenal cortex has been removed can be maintained in good health if cortin is injected daily. They can be kept in good condition for long periods of time without cortin if the diet is high in sodium chloride and low in potassium. However, animals maintained only by diet adjustment develop low blood sugars and become acutely ill during periods of fasting.

If the adrenal cortex of a human being becomes underactive (usually as a result of tuberculosis of the adrenals), the resulting condition is known as *Addison's disease.* This disease is characterized by the biochemical changes already mentioned. In addition, the blood pressure is low, marked weakness is present, and a characteristic pigmentation of the arms, face, and upper part of the body appears. The excess pigment appears to be melanin (see page 654).

Overactivity of the adrenal cortex is due usually to a tumor, the cells of which produce excess hormones. If such a tumor develops in childhood, sexual development is hastened. Overactivity in adult life is most commonly found in the female. Females with adrenal tumors become more masculine in appearance: hair appears on the face, the voice deepens, and the breasts decrease in size. In the case of adult males, masculine characteristics are accentuated.

Hormone of the Thyroid Gland.—The thyroid gland is composed of two lobes, joined by a strip of tissue called the isthmus. The entire structure is in the front part of the neck, just below the larynx (voice box). When the gland is examined with the aid of a microscope, it is found to be composed of connective tissue, in which are embedded many small, spherical structures, the *follicles.* Each follicle is filled with a colloidal material, composed chiefly of water and the characteristic protein of the thyroid, *thyroglobulin.* One of the amino acids produced when thyroglobulin is hydrolyzed is *thyroxine.* This amino acid often is considered the hormone of the thyroid gland, although it is possible that it must become incoporated into a protein molecule before it has physiological activity. It is believed that thyroxine is made in the body from tyrosine and iodine.



Thyroxine

It appears to be the function of thyroxine to speed up the rate of metabolism of all the cells of the body. The most obvious effect produced by removal of the thyroid gland is a decrease in energy (heat) production by all the tissues of the animal. Conversely, the injection of thyroxine causes a rise of body heat output. It has been estimated that 1 mg. of thyroxine can result in an increase of metabolism equivalent to about 3,000 large calories. The increased energy production does not begin to manifest itself until several hours after the injection (perhaps this is the time required for the amino acid to become a part of a protein molecule) and the effect of a single dose lasts for several days.

Some of the biochemical changes caused by removal of the thyroid gland are summarized below:

(1) The rate of production of energy is decreased.

(2) The level of blood iodine is lowered.

(3) The level of blood lipids, especially cholesterol, is elevated.

(4) The rate at which sugar is deposited as glycogen in the tissues following a meal is increased.

(5) The excretion of calcium, phosphates, and nitrogen is decreased.

(6) The excretion of creatine by young animals or children is decreased. It will be recalled that creatine is a normal component of the urine in childhood, although it is found only in small amounts in the urine during adult life.

(7) There is an abnormal storage of protein in the body fluids.

Injections of thyroxine produce effects opposite to those just summarized. Thus, the excretion of calcium, phosphates, and nitrogen increases; the level of blood lipids decreases; the rate of energy production increases; the level of blood iodine increases; creatine apppears in increased amounts in the urine of adults; and glucose is deposited as glycogen more slowly. This last effect appears to indicate that thyroxine antagonizes to some extent the action of insulin.

Fig. 80.—An adult cretin. Compare the height of the woman with that of the cattle. What is the cause of cretinism? (Courtesy of Dr. J. F. McClendon.)

An enlarged thyroid gland is called a *goiter*. Goiter ordinarily accompanies both overactivity and underactivity of the thyroid. Severe thyroid underactivity in infancy is called *cretinism*. The mental and physical development of cretins is retarded. They grow up to become dwarfs, with short, broad bodies; wide, flat noses; and coarse, dry hair. The skin is thick, inelastic, and dry. Many cretins are idiots. Marked underactivity in adult life is known as *myxedema.* In this condition the temperature is below normal; the tongue is thick and dry; the pulse rate is slow; and the skin is filled with a thick, protein-containing material. The decreased rate of burning of food causes an increase in weight, usually in spite of a poor appetite.

Many people who live in regions of the United States in which the surface water is low in iodine have goiters, but most of them do not show signs of thyroid gland disease.

People who have overactive thyroid glands tend to be warm when others are cool; they lose weight in spite of an increased appetite; and they are extremely nervous. Weakness often is a prominent feature. In some instances, the eyeballs bulge forward (exophthalmos), in which case the person is said to have *exophthalmic goiter.*

It has been found recently that certain organic compounds (some sulfonamides, thiourea, thiouracil, propyl thiouracil, and others) interfere with the production of thyroxine by the thyroid gland, even in the presence of an abundance of iodine. When these substances are administered to laboratory animals or to human beings, the signs and symptoms of underactivity of the thyroid gland appear. Certain of them, especially propyl thiouracil, are used in the therapy of hyperthyroidism (thyroid overactivity).

Another interesting finding is that certain proteins, such as casein and serum albumin, can be made to combine with iodine in such a way that thyroxine is formed in the intact protein molecule. Such iodinated proteins are potent substitutes for the natural hormone of the thyroid. It has been reported that the administration of iodinated casein to milk cows results in an increased yield of milk and butter fat.

Hormone of the Parathyroid Glands.—The parathyroid glands are attached to the posterior part of the thyroid gland. Usually there are four of them. They are very small, and their combined weight is only about 120 mg.

The hormone of the parathyroid gland is called *parathormone*. It is a protein, and its activity is destroyed by peptic or tryptic digestion. It has not yet been isolated in pure form.

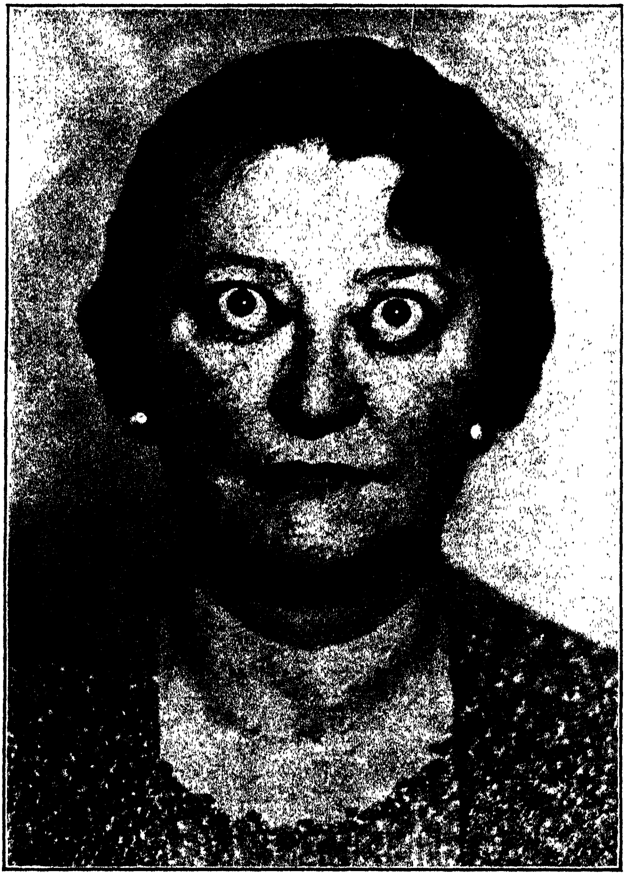


Fig. 81.—Photograph of a woman with exophthalmic goiter. What is thought to be the cause of this condition? (From Meakins: The Practice of Medicine, The C. V. Mosby Co.)

Removal of the parathyroid glands, or destruction of them by disease, causes: (1) a fall in the level of plasma calcium; (2) a rise of the level of plasma inorganic phosphorus; (3) and a decrease in the excretion of calcium in the urine. The low plasma

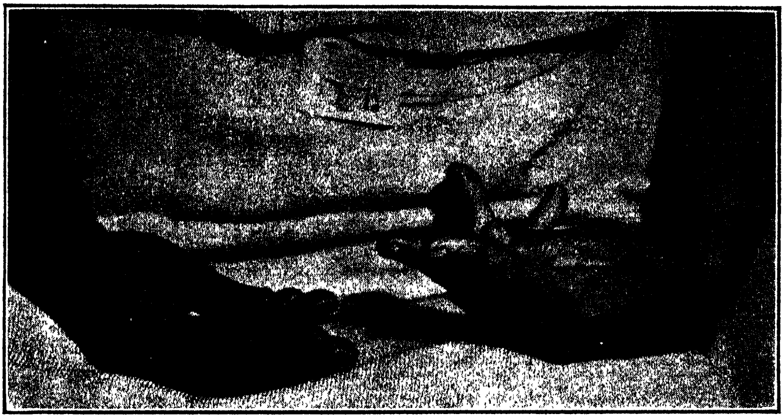


Fig. 82.—Photograph illustrating tetany (spasmodic muscular contractions) caused by underactivity of the parathyroid glands. What hormone is manufactured by these glands? (From Meakins: The Practice of Medicine, The C. V. Mosby Co.)

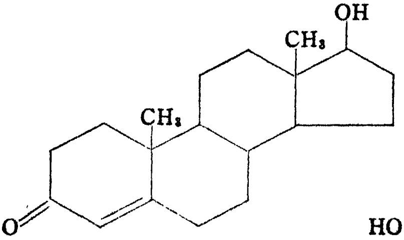
Fig. 83.—X-ray photograph of the arm of a person suffering with overactivity of the parathyroid glands. Notice that large areas in the bones do not photograph well. This indicates the presence of areas of decalcification (loss of the bone minerals). What type of organic compound is parathormone? (From Meakins: The Practice of Medicine, The C. V. Mosby Co.)

calcium level is accompanied by tetany (convulsions). Death occurs unless calcium salts in large amounts, or injections of parathormone, are given.

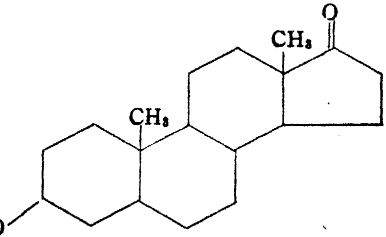
Parathyroid overactivity is due ordinarily to an adenoma involving one or more of the glands. The excessive secretion of hormone by the tumor cells causes: (1) an increase in the level of plasma calcium; (2) a decrease of the level of plasma inorganic phosphorus; and (3) an increased excretion of calcium and phosphorus in the urine. Calcium and phosphorus appear to leave the bones and to pass out of the body in the urine. In human beings the disease known as *osteitis fibrosa cystica* may result. This condition is characterized by an extensive decalcification of the bones, which become soft and easily crushed or broken.

It is assumed that parathormone functions in the normal person as a regulator of the exchanges of calcium (and phosphorus) between the bones and the tissue fluids. In this manner, it regulates the level of blood plasma calcium.

Hormones of the Testes.—The testes are oval structures located in the scrotum of the male. Each testis contains many coiled ducts, the linings of which manufacture the male sex cells (spermatozoa). Between the ducts are large cells known as *interstitial cells.* The interstitial cells make a hormone called *testosterone.* Testosterone has been isolated from the testes only. However, two other male sex hormones, *androsterone* and *dehydroisoandrosterone,* are excreted in the urine. Probably androsterone is made in the body from testosterone.



Testosterone



Androsterone

The male sex hormones are responsible for the development of the secondary sex characters at the time of puberty: the growth of hair on the face and body, the deepening of the voice, and so on. They also regulate the growth and function of certain glands (prostate gland, Cowper's glands, seminal vesicles) associated with the reproductive system of the male.

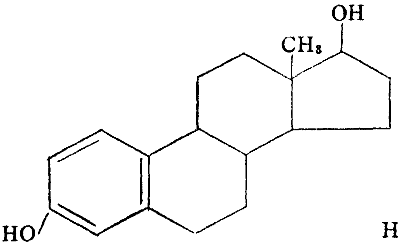
When the testes are removed from young animals, the creatine content of the muscles decreases, and the amount of fat in the muscular tissue increases. These changes improve the quality of the meat obtainable from the adult animal.

Small amounts of male sex hormones are present in the urine of females. Presumably they are made in the ovaries and adrenals.

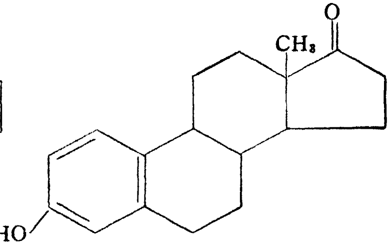
Hormones of the Ovaries.—The two ovaries are small, almond-shaped structures located in the pelvic (lower abdominal) cavity of the female. At birth they contain numerous immature ova (eggs). After the age of puberty, and before the menopause (change of life), an ovum normally matures and is discharged into the pelvic cavity at intervals of about four weeks. During this maturation process the ovum becomes attached to the wall of a small, spherical cavity, called the *follicle.* Just prior to ovulation (discharge of the ovum into the pelvic cavity), the follicle moves to the periphery of the ovary; at ovulation it ruptures, and the ovum is released. If the first day of the menstrual period is taken as the first day of a complete menstrual cycle, ovulation ordinarily occurs about the thirteenth or fourteenth day, and a new cycle begins on the twenty-ninth day.

The cells that line the developing follicle (follicular cells) manufacture substances known as *follicular hormones,* or *estrogenic hormones.* The word *estrogenic* is used because these hormones are responsible for the periodic occurrence of estrus (the period during which the female is capable of mating) in the lower animals. Two hormones, *estrone* (theelin) and *estradiol* (dihydrotheelin), have been isolated from the fluid within the ovarian follicles and from the urine of pregnant animals. A third compound, *estriol* (theelol), has been isolated from urine, but not from the ovary. Of the three substances, estradiol is most active physiologically, and estriol is least active. It is supposed that estradiol is the substance first made by the follicular cells, and that estrone then is made from it. Apparently, estriol can be made from estrone by the lining of the uterus (womb) during the second half of the menstrual cycle.

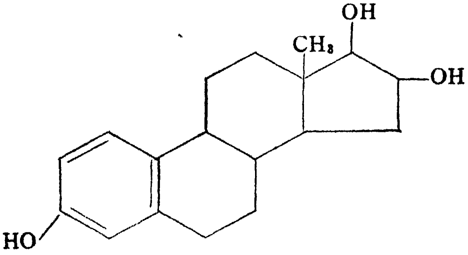
The follicular hormones are responsible for the changes (development of the breasts, appearance of body hair, and so on) that occur at the time of puberty. During the first half of the menstrual cycle they are excreted in the urine. After ovulation the amount of them present each day in the urine decreases, but there is a secondary increase and decrease of excretion before the beginning of a new cycle (see Fig. 84).



Estradiol



Estrone



Estriol

After the expulsion of the ovum from the follicle, the follicular cavity becomes filled with a blood clot. This clot soon is invaded by cells, forming a yellow structure called the corpus luteum (yellow body). The corpus luteum ordinarily is replaced by scar tissue in about twelve days, although, if pregnancy occurs, it persists for six to nine months. The cells of the corpus

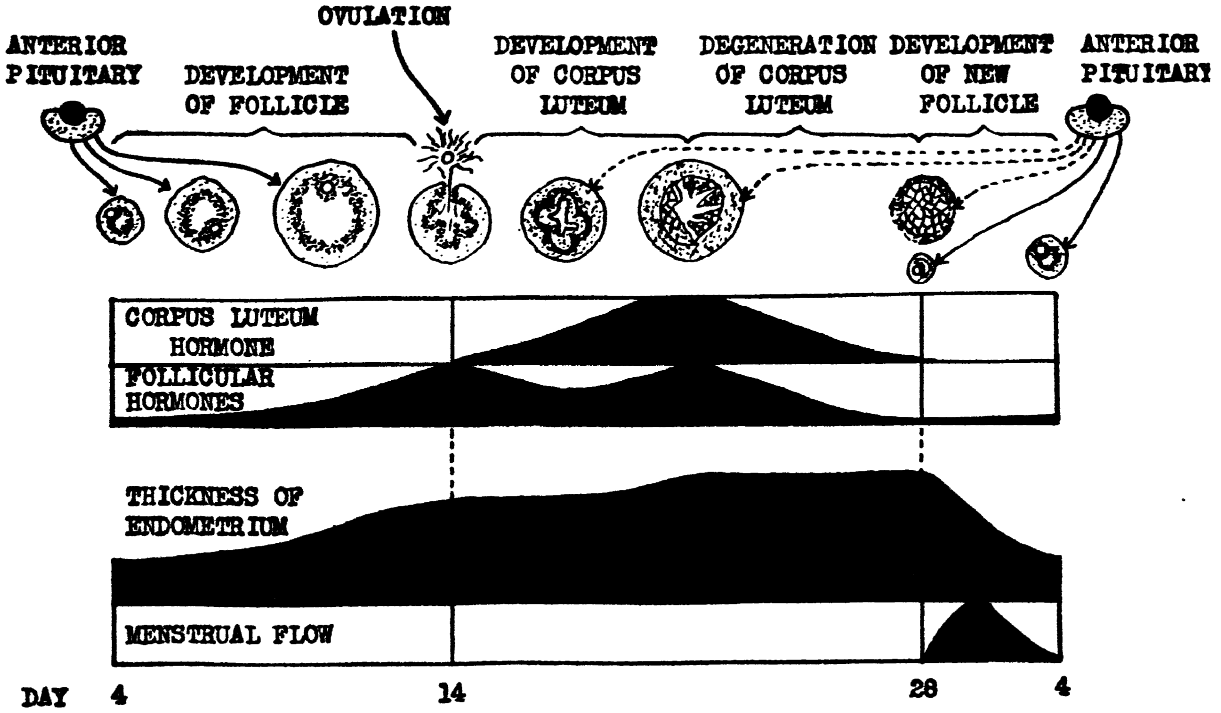
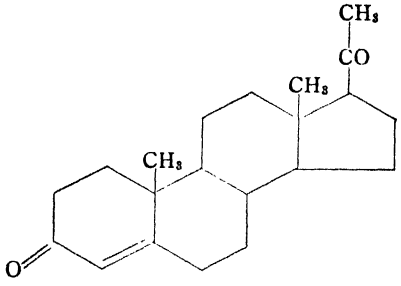
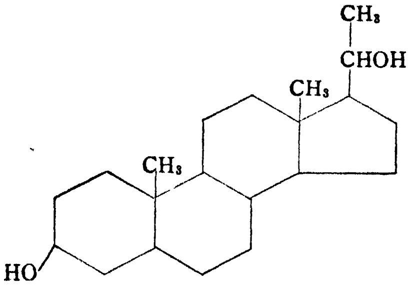


Fig. 84.—Diagram to show the endocrine control of the endometrium (lining of the uterus). What pituitary hormones help regulate the production of ovarian hormones? (Adapted from a drawing in color supplied through the courtesy of Parke, Davis & Co.)

luteum make a hormone known as *progesterone.* Probably estrogenic hormones also are made by these cells. Progesterone is changed in the body to an inactive compound, *pregnanediol.* Pregnanediol then combines with glycuronic acid (an organic acid chemically related to glucose), and is excreted in combined form in the urine. This substance is present in the urine only during the latter half of the menstrual cycle.



Progesterone



Pregnanediol

Most of the endometrium (lining of the uterus) sloughs off and is discharged during the menstrual period. During the first half of the cycle following menstruation, the endometrium grows again. This period of growth is caused by the follicular hormones. During the second half of the cycle, progesterone is secreted by the corpus luteum. This hormone causes the endometrial glands to grow and to fill with secretion; the endometrium becomes engorged with blood, and cells that will help form the placenta, if pregnancy takes place, make their appearance. In other words, progesterone appears to prepare the endometrium for the reception of a fertilized ovum. If fertilization does not occur, the excretion of follicular and corpus luteum hormones becomes very small, and a new menstrual period follows. In the event that pregnancy takes place, the corpus luteum does not become replaced by scar tissue for several months, and the excretion of follicular hormones and pregnanediol in the urine gradually increases until a few days prior to the onset of labor. At this time, excretion of these hormones falls off, and labor soon follows.

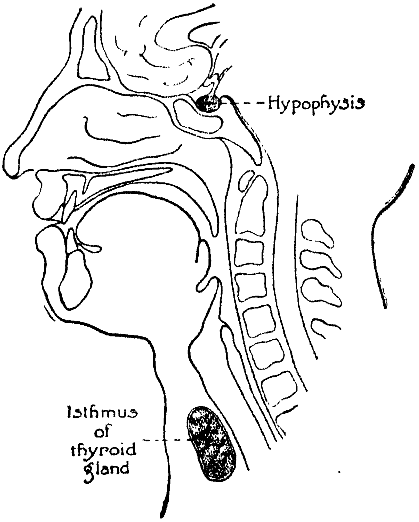


Fig. 85.—Drawing to show the location of the pituitary gland (hypophysis). Why is the anterior lobe of this gland sometimes called the "master gland" of the endocrine system? (From McClendon and Pettibone: Physiological Chemistry, The C. V. Mosby Co.)

The ovarian hormones also cause the enlargement of the breasts that takes place during pregnancy. It is probable that a hormone made by the pituitary gland (the mammogenic hormone) has a similar function. Ovarion hormones are elaborated by the placenta, as well as by the ovary, during pregnancy.

Small amounts of follicular hormones are present in the urine of males.

Hormones of the Pituitary Gland.—The pituitary gland (hypophysis) is a small structure attached to the base of the brain by means of a stalk, the *infundibulum.* It is composed of an *anterior lobe,* a *posterior lobe,* and an intermediate strip of tissue, the *pars intermedia.*

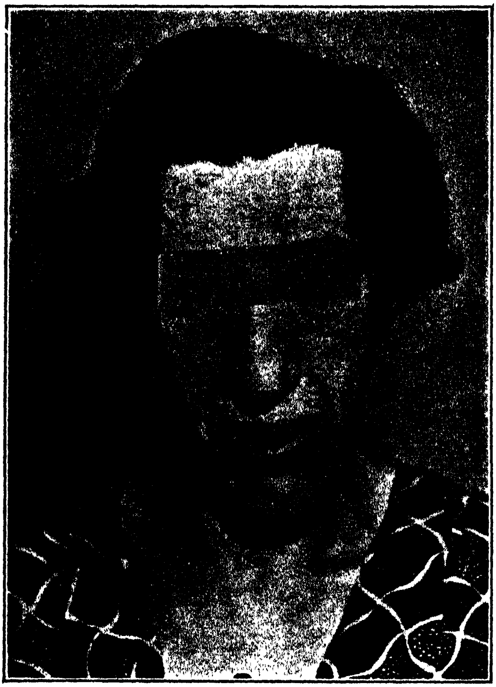


Fig. 86.—Photograph of a person who has acromegaly. What is the cause of this condition? (From Meakins: The Practice of Medicine, The C. V. Mosby Co.)

Hormones of the anterior lobe. The anterior lobe has been called the master gland of the endocrine system, because several of its hormones are necessary for the proper functioning of other ductless glands. The anterior lobe hormones are proteins, and are ineffective if administered by mouth.

1. *Growth hormone.* This substance is necessary for normal growth of young animals. It is a globulin, and is readily destroyed by acids or alkalies. When it is injected into animals, it

causes an increased storage of protein, water, calcium, and phosphorus. If it is made in insufficient amounts during childhood, the person becomes a dwarf. Most circus dwarfs have underactive pituitary glands. If an adenoma of the anterior lobe develops during childhood, excessive amounts of growth hormone may be produced, and the person grows up to be a giant. Excessive production of the hormone during adult life causes *acromegaly*. This condition is accompanied by marked enlargement of the jaw, hands, and feet. Curvature of the bony spine also is present.

2. *Gonadotrophic hormones.* These hormones regulate the production of sex hormones. The *follicle-stimulating hormone* (F.S.H., thylakentrin) has a polysaccharide prosthetic group, and its activity is destroyed by salivary amylase or intestinal polypeptidase. It stimulates the production of the follicular hormones by the ovary. In the male it is necessary for proper functioning of the cells that manufacture the spermatozoa (sex cells).

The *luteinizing hormone* (L.H., metakentrin) is made inactive by pepsin and trypsin, but is not affected by amylase. In the female it stimulates the production of progesterone by the corpus luteum, and, in the male, the production of male sex hormones by the interstitial cells of the testes.

During pregnancy the placenta makes a substance that causes effects similar to those brought about by the gonadotrophic hormones. This placental hormone usually is termed *chorionic gonadotrophin* but is known also as the *anterior-pituitary-like factor* (A.P.L., or prolan). It appears in the urine shortly after pregnancy begins. If the urine of a pregnant female is injected into the blood of an immature female rabbit, an ovarian follicle filled with a blood clot appears forty-eight hours later. This is the basis of a common test for pregnancy.

3. *Thyrotrophic hormone.* This hormone stimulates growth of the thyroid gland and increases the output of thyroid hormone. Exophthalmos also can be produced in experimental animals by injecting large amounts of it. Many scientists believe that exophthalmic goiter may be caused, in part at least, by an increased secretion of the thyrotrophic hormone.

The active substance is a globulin. Its activity is destroyed by heat or by peptic digestion.

4. *Adrenotrophic hormone.* This substance probably is a polypeptide. It can be precipitated from water solution by alcohol, but it is soluble in water solutions one-third saturated with ammonium sulfate. In its absence the cortex of the adrenal gland decreases in size. The cortical underactivity that also results causes more impairment in carbohydrate metabolism than in water and salt metabolism.

5. *Lactogenic hormone (prolactin).* A globulin with the properties of this factor has been isolated in crystalline form from extracts of the pituitary gland. Following the decreased production of ovarian hormones at the termination of pregnancy, this substance becomes active. It is responsible for the formation of milk by the mammary glands (breasts). There is evidence to indicate that the thyroid hormone and the hormones of the adrenal cortex also must be present in the body in proper amounts for normal lactation (milk production).

The following "factors" have not been isolated and are known only by the effects they appear to produce. It is possible that some of the effects actually are due to mixtures of the five hormones just described.

6. *Diabetes-producing factor.* When extracts containing this factor are injected daily into experimental animals, the first effect is a marked stimulation of the isles of Langerhans. After a time, however, the islet cells apparently become exhausted, and insulin production ceases. Animals treated for a sufficiently long period of time with the diabetes-producing factor develop permanent diabetes mellitus.

7. *Ketogenic factor.* If the pituitary gland is removed, fat is not transported from the body stores to the liver at a normal rate. Injection of extracts containing the ketogenic factor increases this transport, and increases (or causes) the formation of ketone bodies by the liver.

8. *Diabetogenic factor.* This factor, when injected into animals, causes a breakdown of liver glycogen and a rise of the blood sugar level.

9. *Glycogenic factor.* When the pituitary gland is removed, the amount of glycogen in the muscles of the body decreases. Injection of the glycogenic factor restores muscle glycogen to its former (or to a higher) level.

10. *Miscellaneous postulated factors.* Factors that control the normal functioning of the parathyroid gland (parathyrotrophic hormone) and the isles of Langerhans (pancreatrophic hormone) have been stated to be made by the anterior lobe. There is evidence that another hormone (the mammogenic hormone), as well as the ovarian hormones, causes an increase in the size of the breasts during pregnancy.

A complete absence or destruction of the anterior lobe causes Simmonds' disease, a condition characterized by premature aging and early death.

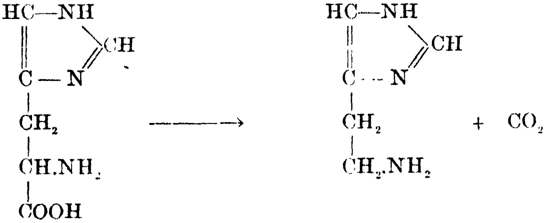
Hormones of the posterior lobe. When *pitressin (vasopressin, β-hypophamine)* is injected into animals, it causes a slow, prolonged increase in blood pressure. This hormone is necessary for the normal reabsorption of water by the kidney tubules. In its absence, diabetes insipidus ("increased flow of insipid urine") results. Patients with diabetes insipidus may excrete 20 or more liters of urine each day. In one recorded case, the daily excretion amounted to 50 liters.

Pitocin (oxytocin, α-hypophamine) causes a contraction of the smooth muscle of the uterus when it is injected. It is used frequently after childbirth; the contraction of the uterine muscle caused by its administration assists in controlling bleeding. After an injection of this hormone, there are an increased rate of liver glycogen breakdown and a rise of the blood sugar level. Pitocin causes also a contraction of the smooth muscle fibers that surround the alveoli of the milk ducts of the breast, thus permitting an easier release of the milk present in the gland (breast).

Hormone of the pars intermedia. The pars intermedia contains a substance called *intermedin.* Intermedin causes a dilation of the pigment spots present in the skins of some of the lower animals. It has not yet been shown to have a function in human physiology.

Hormones of the Digestive Tract.—1. *Antianemic principle.* The lining of the stomach manufactures a substance known as the *intrinsic factor.* This factor probably is an enzyme. When another substance, known as the *extrinsic factor,* and found in foods, enters the stomach, it reacts in some unknown manner with the intrinsic factor. The product produced by this reaction is a third substance, called the *antianemic principle.* This principle, which is necessary for the proper formation and release of red blood cells by the bone marrow, is stored in the liver. People who are unable to make the intrinsic factor also cannot prepare the antianemic principle, and suffer from the disease known as pernicious anemia. Persons with this disorder are treated by means of injections of extracts of liver that contain the stored antianemic principle. (See Vitamin B_{12}, page 721.)

2. *Gastrin* is manufactured by the pyloric end (end nearest the duodenum) of the stomach. It causes an increased secretion of gastric juice and an increase in the motility of the stomach. It is believed by some biochemists that gastrin is identical with histamine, a substance made in the body from the amino acid histidine.


Histidine Histamine

3. *Secretin.* When hydrochloric acid enters the small intestine from the stomach, it causes the conversion of a substance present in the intestinal cells *(prosecretin)* to *secretin.* The secretin thus formed causes a secretion of pancreatic juice.

4. *Enterogastrone.* This substance is secreted by the small intestine when fat or concentrated sugar solutions enter from the stomach. It decreases the secretion of hydrochloric acid by the stomach. The motility of the stomach also is lessened.

5. *Cholecystokinin.* This substance is made by the small intestine when fat is present. It causes a slow contraction of the gall bladder, and, consequently, a discharge of bile into the duodenum.

6. *Enterocrinin* is a substance that stimulates a flow of intestinal juice (succus entericus). It is made by the intestinal cells.

The Renin Mechanism.—The pulse pressure (difference between the highest and lowest arterial pressures during one heartbeat) of the kidney arteries can be reduced by appropriate surgical procedures. One such procedure involves placing a metal clamp around the renal artery in such a way that the vessel is partly, but not completely, occluded. The same effect can be obtained by wrapping the kidney with a sheet of cellophane, silk, or cotton. This latter procedure causes the formation of scar tissue around the kidney; this hard, fibrous tissue contracts and "squeezes" the kidney arteries. When the arterial pulse pressure in the kidney is reduced by either of these methods, the animal develops hypertension (high blood pressure). The sequence of biochemical events leading to this development of hypertension appears to be as follows: As a result of the lowered pulse pressure, the kidney cells produce and release into the blood a protein known as *renin.** Renin appears to be an enzyme, and it catalyzes the formation of a polypeptide, *angiotonin* or *hypertensin,* from one of the serum globulins (*renin activator* or *hypertensinogen*). Angiotonin is thought to be the substance actually responsible for the rise of blood pressure. Substances capable of inactivating both renin and angiotonin are present in blood and other tissues. Certain kidney extracts have been claimed to lower the abnormally high blood pressure caused by the surgical procedures described above. Numerous scientists have expressed the view that one type of hypertension in human beings is due to kidney disease.

Plant Hormones.—Certain substances, elaborated by plants, are able to modify and control plant growth. These substances are analogous in some respects to the hormones found in animals, and frequently are known as *plant hormones.* Many other names (plant growth substances, plant vitamins, phytamins, ergones, auxithals, nutrilites, growth factors, growth activators. and so on) have been used for them.

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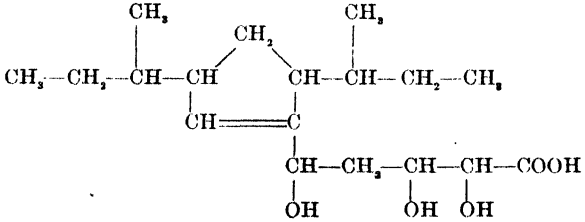
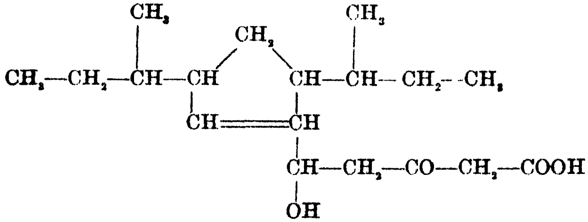
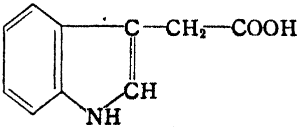
*Do not confuse the enzyme *renin (rē'nin)* with the enzyme *rennin (rĕn'nin),* which was discussed in Chapter XXVI.

Suppose the tip of the coleoptile (first leaf sheath) of a young seedling oat plant is cut off. This procedure removes most of the oat plant hormones, which are concentrated in the growing tip. If now the tip of a growing coleoptile (which contains plant hormones) is applied to one side of the cut surface, the cells on that side grow larger than those on the other side. As a result, the cut coleoptile bends to one side because of the unequal growth. This type of experiment often is used in testing materials in order to find out whether or not they contain plant hormones.

When a hormone is injected into an animal, it is distributed rapidly throughout the entire animal by the blood stream, and tissues distant from the site of injection often are affected. How-


Auxentriolic acid


Auxenolonic acid


Indole-acetic acid

ever, plant hormones diffuse only slowly from one plant cell to another, usually in a vertical direction, and the effects exerted by them often are confined to the immediate vicinity of the site of application.

Plant hormones are of commercial importance, since they can cause rootings to appear on cuttings of plants more rapidly than normal. It is possible also to cause roots to grow from stems or leaves of plants by applying hormones, but this phenomenon is of no commercial importance.

Strangely enough, one of the best natural sources of plant hormones is urine. Apparently, plant hormones taken into the animal body with plant foods are eliminated, in part at least, in the urine. Three of the active substances that have been isolated in crystalline form from urine are auxentriolic acid (auxin a), auxenolonic acid (auxin b), and indole-acetic acid (heteroauxin, rhizopin).

Auxentriolic acid and auxenolonic acid occur in the growing tips of higher plants. Indole-acetic acid has not been proved to occur in higher plants, but it has been isolated from yeast. Many synthetic substances chemically related to indole-acetic acid are effective in stimulating or controlling plant growth.

A number of the water-soluble vitamins (see Chapter XXIX) have been found to stimulate the growth of many lower forms of plant life (yeasts, molds, fungi, bacteria, algae). Numerous workers have reported that thiamine (vitamin B_1) accelerates and increases the growth of certain of the higher green plants. Some investigators have disputed this claim.

Traumatic acid (1-decene-1,10-dicarboxylic acid) increases cell division and healing of the cut surfaces of some plants. It promotes the growth of certain algae.

Study Questions

1. Define: hormone, endocrine gland. How does an endocrine gland differ in structure from one of the digestive glands?
2. What cells manufacture insulin? Who first prepared active solutions of this substance?
3. What is the chemical nature of insulin? What chemical groups in its molecule cannot be altered without causing a loss of physiological activity?

4. What is the usual cause of diabetes mellitus? What biochemical abnormalities are associated with diabetes mellitus?
5. List the biochemical changes caused by the injection of insulin into diabetic and normal animals.
6. List the supposed functions of insulin.
7. What symptoms accompany hyperinsulinism?
8. What is lipocaic?
9. What hormone is made by the adrenal medulla? From what amino acid is this substance believed to be derived?
10. What effects can be produced by injecting adrenaline into an animal? Are these effects of any advantage to the person?
11. What is cortin?
12. List the important biochemical abnormalities produced by removal of the adrenal cortex from an animal.
13. How can animals from which the adrenals have been removed be maintained in good health?
14. What is Addison's disease?
15. What are the usual effects of overactivity of the adrenal cortex?
16. What name is given to the characteristic protein of the thyroid gland?
17. What is thyroxine? What is its most important function?
18. List the important biochemical changes produced by removal of the thyroid gland. What changes are caused by overactivity of the gland?
19. Define: goiter, cretinism, myxedema, exophthalmic goiter.
20. What name is given to the hormone of the parathyroid glands? What is its chemical nature?
21. List the biochemical changes that accompany underactivity and overactivity of the parathyroid glands.
22. What is the probable function of parathormone in normal metabolism?
23. What cells manufâcture the male sex hormones?
24. Name the three most important androgenic (male sex) hormones.
25. What are the functions of the male sex hormones?
26. Name the three follicular hormones of the ovary. List their functions.
27. What is the chemical nature of the sex hormones?
28. What hormone is made by the corpus luteum?
29. In what form is progesterone excreted in the urine of females?
30. What are the functions of progesterone?
31. Correlate the excretion of female sex hormones in the urine with the various phases of the menstrual cycle.
32. What gland manufactures the growth hormone? What is the chemical nature of the hormones manufactured by this gland?
33. What are the effects of overproduction of this substance (the growth hormone)? Of underproduction?
34. List the functions or effects caused by each of the following pituitary hormones: gonadotrophic hormones, thyrotrophic hormone, adrenotrophic hormone, lactogenic hormone, diabetes-producing factor, ketogenic factor, diabetogenic factor, glycogenic factor.

35. What is chorionic gonadotrophin?
36. What is the cause of Simmonds' disease?
37. Name the hormones made by the posterior lobe of the pituitary gland. What effects are produced by injecting them into animals?
38. What is the cause of diabetes insipidus?
39. What is intermedin?
40. List the hormones of the digestive tract. Indicate the function of each of them.
41. What is meant by the term *plant hormone?* Name three plant hormones that have been isolated from urine.
42. Explain how the coleoptile of a young seedling oat plant can be used in testing for the presence of plant hormones.
43. Why are plant hormones of commercial importance?
44. What substances important in animal nutrition act as plant hormones for the lower forms of plant life?
45. What is traumatic acid?
46. What is renin? Under what circumstances is it thought to be produced by the kidney?
47. What substance is thought to be responsible for the hypertension that follows partial occlusion of the renal artery?

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CHAPTER XXIX

VITAMINS

Introduction.—From a physiological point of view, vitamins are similar to hormones. That is to say, vitamins are necessary for normal metabolism. Only small amounts of them are required each day, and presumably they act as components of the various enzyme systems that catalyze metabolic reactions. Unlike hormones, however, the vitamins or their provitamins must be present in the diet. Provitamins are substances that can be converted to active vitamins in the tissues.

In 1911 Funk isolated what he believed to be a pure substance that was effective in preventing or curing the disease of pigeons known as polyneuritis. This material, which contained nitrogen and seemed to be essential for life, was termed "vitamine" (vital amine). It soon was realized that many food factors essential for normal metabolism did not contain nitrogen, and the final "e" employed by Funk was dropped. Today, there is a growing tendency to drop the vitamin terminology altogether, and, wherever possible, to designate the vitamins by appropriate chemical names instead of by letters of the alphabet.

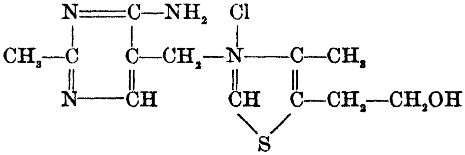
THE WATER-SOLUBLE VITAMINS

The Vitamin B Complex

The first water-soluble vitamin to be recognized was the factor now known as thiamine, or vitamin B_1. It soon became evident, however, that other water-soluble factors were associated with thiamine, and the term *vitamin B complex* was coined. The vitamin B complex consists of all the water-soluble vitamins except ascorbic acid and, perhaps, citrin. Many biochemists do not believe that citrin should be regarded as a vitamin (see page 724).

Thiamine.—Thiamine (vitamin B_1, aneurin) is a white, crystalline solid. It contains a free amino group and, therefore, can react with mineral acids to form salts. Thiamine hydrochloride is soluble in water, slightly soluble in absolute alcohol, and almost insoluble in ether and benzene. When it is dry, it is resistant to prolonged heating at 100° C. Heating it in alkaline solution rapidly destroys its physiological potency.

Thiamine was synthesized by Williams and Kline in 1936.



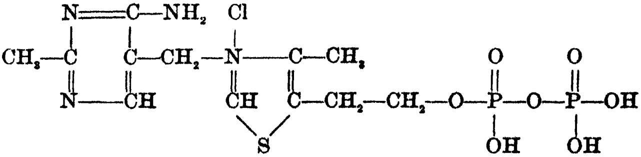
Thiamine chloride

Severe thiamine deficiency in the human being causes the disease known as *beriberi.* The most characteristic symptom of this condition is polyneuritis, or multiple involvement of the peripheral nerves of the body. At first these nerves are painful, especially when pressure is applied. Later, paralysis develops in the muscles supplied by the involved nerves, and the muscles atrophy (decrease in size) from disuse. The heart dilates and enlarges, and death may result from heart failure. Many cases of beriberi are accompanied by edema.

Milder thiamine deficiency in human beings or animals is accompanied by failure of growth, loss of appetite, and pain along the course of the peripheral nerves. The vitamin is believed to be necessary for the normal production of milk by nursing animals.

Thiamine is absorbed readily from the intestinal tract, and small amounts of it are excreted each day in the urine. Apparently only small amounts of it can be stored in the animal organism, because deficiency symptoms ordinarily appear in from ten to thirty days after removal of the vitamin from the diet.

In the tissues thiamine is converted to its pyrophosphate ester.



Thiamine pyrophosphate (Cocarboxylase)

Thiamine pyrophosphate is a coenzyme for the decarboxylation (removal of CO_2 from the —COOH group) and oxidation of pyruvic acid in the tissues. It will be recalled that pyruvic acid is formed during the metabolism of carbohydrates (see Chapter XXIV). One of the characteristic biochemical changes accompanying thiamine deficiency is an elevation of the level of pyruvic acid in the blood of the deficient animal. It has been suggested that thiamine also may be necessary for the conversion of carbohydrate to fat in the body.

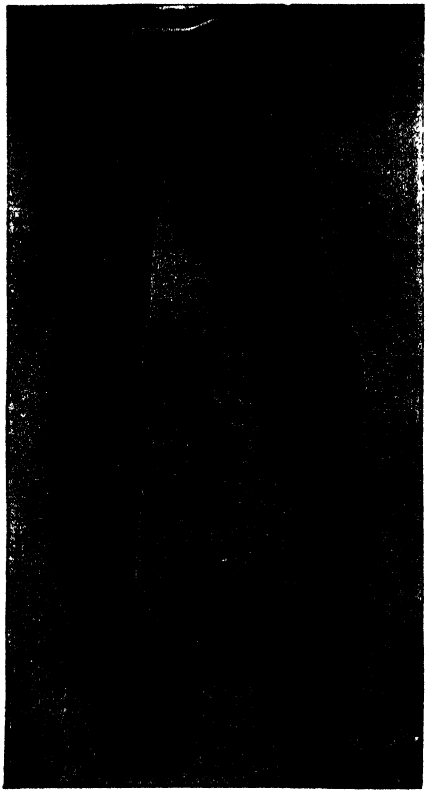


Fig. 87.—Photograph illustrating beriberi. Notice the wasting of the muscles and the weakness of the feet. What is the cause of beriberi? (From Stitt: Diagnosis and Treatment of Tropical Diseases, P. Blakiston's Son & Co.)

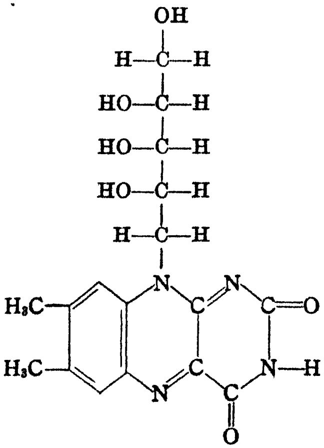
An international unit (I. U.) of thiamine is equivalent in activity to 0.003 mg. of crystalline thiamin hydrochloride. The recommended daily intake of the vitamin for adults is 1 to 2 mg. and for growing children is about 0.4 to 1.8 mg. depending on age. During pregnancy and lactation (milk secretion) the requirement is higher, 1.8 to 2 mg. daily.

The richest source of most of the members of the vitamin B complex, including thiamin, is brewer's yeast. Liver, eggs, legumes, nuts, and whole grains are good sources. Leafy vegetables and fruits are poor sources.

Ordinary cooking procedures do not destroy appreciable amounts of the vitamin, unless sodium bicarbonate is present in the cooking water. However, it should be remembered that thiamine is water soluble, and thus may be lost in the water used in cooking. Only small losses are caused by canning.

Riboflavin.—In the past, riboflavin has been known by a variety of names. Even today, some workers refer to it as vitamin B_2 or vitamin G. The use of these terms is confusing, however, because older workers used them for crude preparations containing not only riboflavin, but also other members of the vitamin B complex.

Riboflavin exists in the pure state as orange-yellow needles that melt at 292°-293° C. with decomposition. It is slightly



Riboflavin

soluble in water and in alcohol. On hydrolysis it yields a dye (flavin) and a pentose (ribose). It was synthesized almost simultaneously in the laboratories of Karrar and of Kuhn in 1935.

When riboflavin is omitted from the diet of rats, growth ceases, body hair falls out in patches, and cataracts (coagulation of the lens of the eyes) sometimes appear. Its absence from the diet of dogs causes a loss of weight, vomiting, bloody diarrhea, muscular weakness, collapse, and death. The most common deficiency symptoms in man are a dermatitis (skin disorder), cracking of the skin around the corners of the mouth, and keratitis (clouding of the cornea or transparent portion of the eyeball).

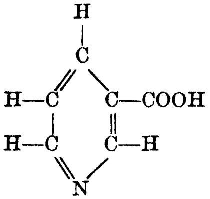
It will be recalled (see page 596) that riboflavin is required for the formation of the flavoproteins that are necessary for normal oxidations and reductions in the tissues. Presumably, the symptoms of riboflavin deficiency are the result of a failure of certain of these oxidative reactions to occur in a normal manner.

The Bourquin-Sherman unit of riboflavin is the amount fed as a daily allowance that induces a gain of body weight of 3 g. per week in an experimental animal (rat) existing on a carefully prepared riboflavin-deficient diet. One Bourquin-Sherman unit is equivalent to about 0.003 mg. of the vitamin. It is estimated that human beings require from 1 to 3 mg. daily.

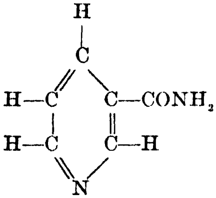
Liver, yeast, lean beef, cheese, eggs, spinach, and wheat germ are good food sources.

Nicotinic Acid.—Nicotinic acid (3-pyridine carboxylic acid) has been known to organic chemists since 1867, but it was not realized that the compound was a vitamin until the work of Elvehjem was published in 1937. When it is pure, it exists as a white, odorless, crystalline powder, which melts at 235°-237° C. It is soluble in water, alcohol, and warm glycerol, but is insoluble in ether.

Apparently, nicotinic acid exists in the body chiefly as nicotinic acid amide (nicotinamide). Nicotinamide is a constituent of the molecules of coenzyme I and coenzyme II (see page 595). It occurs as a white, crystalline powder, which is soluble in water, alcohol, and glycerol. It is very slightly soluble in ether and benzene. Its melting point (129°-131° C.) is considerably lower than that of nicotinic acid.



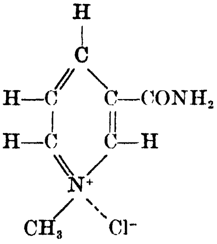
Nicotinic acid (niacin)



Nicotinamide (niacin amide)

The nicotinamide level of the blood of normal persons ranges between 0.5 and 1 mg. per 100 cc. Most of this (about 90 per cent) is present in the red blood cells. There is some evidence that the material present in the plasma is free nicotinic acid, whereas the material in the blood cells is nicotinamide combined in the coenzyme molecule.

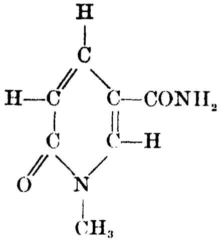
The principal urinary excretory product of nicotinamide apparently is N-methylnicotinamide. This is a quaternary ammonium ion and, as such, can exist in combination with any one of a number of anions.



N-Methylnicotinamide chloride

There is evidence that a portion of the N-methylnicotinamide found in the body is oxidized to N^1-methyl-6-pyridone-carboxylamide.

When the diet of human beings is deficient in nicotinic acid, the disease known as *pellagra* results. In this disease the tip and sides of the tongue are reddened and swollen. A characteristic skin rash, which resembles sunburn, appears on the head, neck,



N_1-Methyl-6-pyridone-carboxylamide

wrists, hands, and, frequently, on the feet and ankles. Mental symptoms (impaired memory, confusion, dizziness, depression) may appear. If the disease is severe, diarrhea usually is a marked symptom.

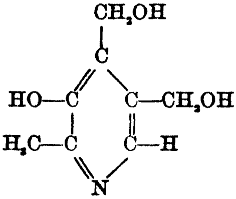
It has been known for many years that pellagra commonly is found in populations that ingest large amounts of corn (maize). Recent studies have shown that corn contains a substance that causes the appearance of a disease resembling pellagra when it is fed to mice or rats. The toxic effect of this unknown substance can be overcome by feeding sufficient nicotinic acid or tryptophan. These observations make it likely that one cause of human pellagra may be the ingestion of large amounts of corn without a corresponding increase in the intake of nicotinic acid. It seems probable also that nicotinic acid can be made in the body from tryptophan, since this amino acid apparently can prevent the appearance of the signs of nicotinic acid deficiency in animals ingesting diets deficient in the vitamin.

Nicotinic acid also is required by dogs, pigs, and many strains of bacteria. The nicotinic acid deficiency disease of dogs is called blacktongue.

Good sources of nicotinic acid are yeast, lean meat, liver, milk, tomatoes, canned salmon, and turnip greens. It is estimated that human being require from 10 to 20 mg. daily.

Pyridoxine.—Pyridoxine (vitamin B_6) is a white, odorless compound, which melts at 157° C. It has a slightly bitter taste. It is readily soluble in water and alcohol, and is slightly soluble in ether and chloroform.

This vitamin has been found to be essential in the diets of rats, pigs, dogs, chicks, and many microorganisms. Deficient rats develop rat acrodynia, a condition characterized by a dermatitis (skin rash) of the paws, nose, lips, chin, and sides of the face.



Pyridoxine

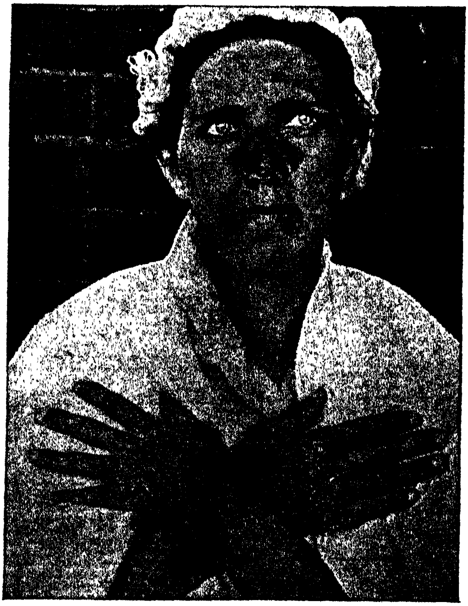
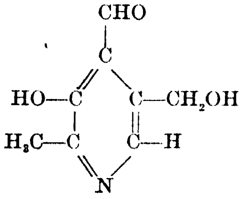


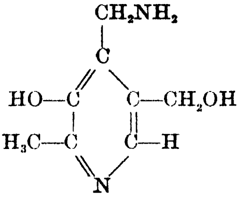
Fig. 88.—Photograph of a person with pellagra. Notice the skin rash. What vitamin prevents this condition? (Courtesy of Dr. G. Leonard Harrington and Dr. Thomas Twyman. From Sutton and Sutton: Diseases of the Skin, The C. V. Mosby Co.)

If the deficiency is continued long, both rats and pigs have epileptiform fits (convulsions, followed by a period of unconsciousness). Pigs and dogs that have been deprived of pyridoxine develop an anemia (low level of hemoglobin and red blood cells in the circulating blood). Pyridoxine is necessary for a normal growth rate of chicks.

Pyridoxal and pyridoxamine are compounds that can be prepared from pyridoxine by relatively simple procedures.



Pyridoxal

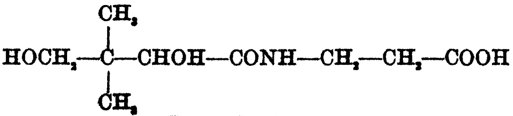


Pyridoxamine

Further research has made it evident that pyridoxal and pyridoxamine can replace pyridoxine in animal diets and in bacterial culture media. Indeed, it seems very probable that pyridoxal is the active form of the vitamin. In the tissues, pyridoxal combines with phosphoric acid, forming pyridoxal phosphate. This latter compound is an important coenzyme for enzyme systems concerned with the decarboxylation of amino acids, transamination, and probably other reactions involving amino acids.

It has not yet been proved that the vitamin is essential in the diet of human beings. It has been used clinically in the treatment of certain muscle diseases and the nausea of pregnancy, but the results are not conclusive.

Pantothenic Acid.—Pantothenic acid is a water-soluble, heat-stable vitamin. It is soluble in ethyl acetate, dioxane, and glacial acetic acid, but is insoluble in ether, benzene, and chloroform. Hot alkalies, hot acids, and cold acid alcohol destroy its physiological potency. The synthetic compound first was prepared in 1940.



$$HOCH_2-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CHOH-CONH-CH_2-CH_2-COOH$$

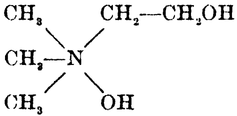
Pantothenic acid

Pantothenic acid is necessary for the normal growth of yeasts, bacteria, mosquito larvae, chicks, rats, and dogs. Chicks develop a severe dermatitis when they are deprived of the vitamin, and it has been reported that pathological changes take place in their spinal cords as a result of the deficiency. When rats are placed on a diet deficient in the vitamin, they cease to grow, pathological changes appear in their adrenal glands, and there is a failure of reproduction.

Human blood contains pantothenic acid (0.02 to 0.03 mg. per 100 cc.), but the role of this substance in human nutrition is not known.

There is evidence that pantothenic acid is a coenzyme for acetylation reactions.

Choline.—Choline is a colorless, viscous, strongly alkaline liquid. It is very soluble in water and alcohol, but is insoluble in ether.



Choline

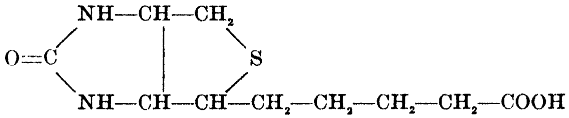
This substance exists chiefly in combined form as a part of the molecules of lecithins and sphingomyelins (see Chapter XII). Certain nerves of the body secrete acetylcholine at their endings, and this compound is responsible for the transmission of nerve impulses from these nerves to other structures (nerves, glands, smooth muscle).

Some nutrition authorities are reluctant to classify choline as a vitamin, because most laboratory animals apparently can synthesize it in their tissues provided sufficient methionine (an amino acid) is present in the diet.

When young rats, are placed on a choline-deficient diet immediately after weaning, they develop a toxic state characterized by kidney hemorrhages (bleeding), a decrease in the size of the thymus gland, and an enlargement of the spleen. Older animals develop fatty livers on the same diet. Apparently, dogs and rabbits also require choline for the prevention of fatty livers.

Chicks placed on a choline-deficient diet develop a condition known as perosis, or slipped tendon.

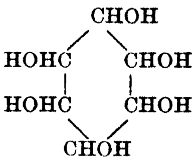
Biotin.—Biotin has been known also as vitamin H and as coenzyme R. It was isolated in crystalline form by Kögl and Tönnis in 1936. It is necessary for the normal growth of yeasts and certain bacteria. Raw egg white contains a protein (avidin) that combines with biotin, thus preventing its absorption. Typical biotin deficiency symptoms can be produced in rats by feeding them a diet containing raw egg white. This deficiency state is characterized by a skin disorder and possibly failure of growth. Biotin is synthesized by bacteria present in the intestinal tract.



Formula for biotin

Biotin and manganese are necessary for CO_2 fixation in plants and animals (see page 618).

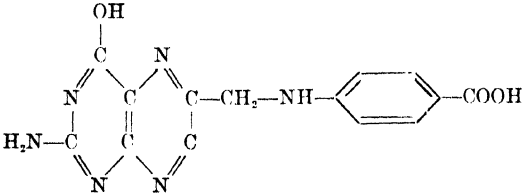
Inositol.—Inositol in the pure state is a white, efflorescent, crystalline substance. It exists in several isomeric forms. It was first isolated from meat in 1850, but its role as a vitamin was not recognized until 1940.



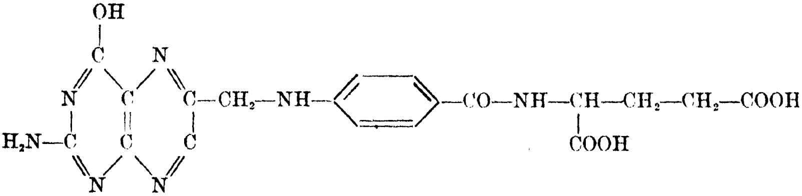
Inositol

Mice cease to grow and become hairless over the trunk when their diet is deficient in inositol. Rats are said to require inositol for the prevention of "spectacled eyes," a condition characterized by a loss of skin and swelling around the eyes. This condition also accompanies biotin deficiency.

Folic Acid Complex.—For a number of years nutritionists have studied a group of unknown substances, apparently related chemically to each other, required by various bacteria and laboratory animals for normal growth and metabolism. Various names, such as folic acid, *L. casei* factor, vitamin B_c, vitamin M, factor U, *S. lactis* R (SLR) factor, and norite eluate factor have been used for one or more members of this group of compounds. It now appears that the members of this "folic acid complex" are pteroic acid, pteroylglutamic acid, pteroyltriglutamic acid, and pteroylheptaglutamic acid.



Pteroic acid

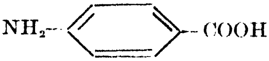


Pteroylglutamic acid (folic acid)

Pteroyltriglutamic acid and pteroylhepatoglutamic acid contain, respectively, three and seven glutamic acid residues per molecule.

Pteroylglutamic acid is required by a number of bacteria. Chicks apparently require it for normal growth and feathering. The most interesting result of deficiency in chicks and laboratory animals, however, is the failure of production of adequate numbers of red and white blood cells. It has been found recently that the vitamin can be used for the relief of some of the signs and symptoms of pernicious anemia. The reason for this is obscure, since liver extracts high in the anti-anemic factor do not appear to contain more than traces of pteroylglutamic acid or related compounds. Unfortunately, however, the vitamin will not prevent the serious neurologic symptoms that sometimes accompany pernicious anemia. There is evidence that the factor may be useful in raising the level of white blood cells in certain pathological states in which there are insufficient white cells in the blood.

One of the substances formed by the hydrolysis of pteroylglutamic acid is *p-aminobenzoic acid.*



p-Aminobenzoic acid

This compound exists as yellowish-red, crystalline needles. It is freely soluble in alcohol, ether, and warm water. It melts at 186°-187° C.

p-Aminobenzoic acid has been found to be necessary for the growth of certain bacteria, and it has been reported that normal growth of rats and chicks does not take place in its absence. One very interesting finding has been the ability of this compound to counteract the effects of the sulfonamide drugs. This has led to the hypothesis that these drugs owe their bacteriostatic properties to their chemical similarity to p-aminobenzoic acid. It is supposed that because of this structural similarity they can attach themselves to some bacterial enzyme required in the metabolism of p-aminobenzoic acid. They are sufficiently different from the latter compound, however, to prevent any further metabolic change. If this hypothesis is correct, sulfonamide drugs prevent the growth of bacteria by blocking the utilization of p-aminobenzoic acid. In the presence of large quantities of this latter compound, the sulfonamide is forced away from the enzyme by mass action; this explains why p-aminobenzoic acid can reverse the bacterial inhibition caused by the sulfonamides.

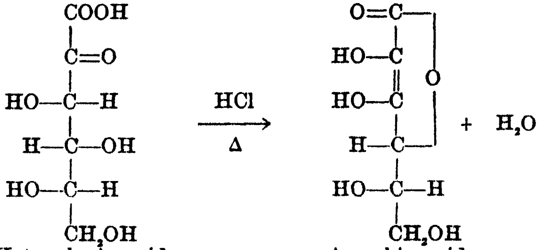
The finding that p-aminobenzoic acid occurs in combined form in pteroylglutamic acid makes it possible that the compound is active in metabolism only in this combined form.

Vitamin B_{12}.—This relatively new factor was isolated in crystalline form in 1948. Preliminary evidence indicates that it may be the long-sought antipernicious anemia principle (see page 702). It may be identical with, or closely related to, the so-called *animal protein factor.* This factor, present in liver but not in yeast, increases the utilization of protein and the rate of growth of deficient animals. Vitamin B_{12} probably has a molecular weight of 1,500 to 2,000 and contains cobalt and phosphorus in its molecule.

Strepogenin.—It has been found that tryptic digests of some, but not all, proteins contain a factor that stimulates the growth of certain bacteria. This same factor has been found to stimulate the growth of laboratory animals, such as mice. Since proteins are believed to be composed mainly of amino acids linked to each other by peptide bonds (see page 559), it has been postulated that this unknown substance is a peptide that exists as an integral part of the protein molecule. When the protein is digested with trypsin, presumably the active peptide is released. This theory is strengthened by the finding that activity is lost if digestion in the presence of trypsin is allowed to proceed too far. This growth factor has been given the tentative name, *strepogenin,* since it stimulates the growth of certain streptococci (bacteria). Casein and crystalline trypsinogen are good sources of strepogenin. Egg white, which contains protein of very high nutritional quality, is a poor source of the factor.

Ascorbic Acid

Ascorbic acid (vitamin C, cevitamic acid) is the lactone prepared by treating 2-ketogulonic acid with hydrochloric acid. The pure material occurs as white, odorless crystals or as a crystalline powder. It melts at 190°-192° C. It is soluble in water and, to a limited extent, in absolute alcohol and glycerol, but is insoluble in benzene, chloroform, ether, petroleum ether,



2-Ketogulonic acid   Ascorbic acid

and fats. It is stable when dry, but deteriorates rapidly in water solution, especially if the solution is alkaline. It is a relatively strong reducing agent.

The cells of the body are cemented together by a material called the *intercellular substance.* Ascorbic acid appears to be essential for the formation and maintenance of this material. Probably the vitamin also plays a role in tissue oxidations and reductions.

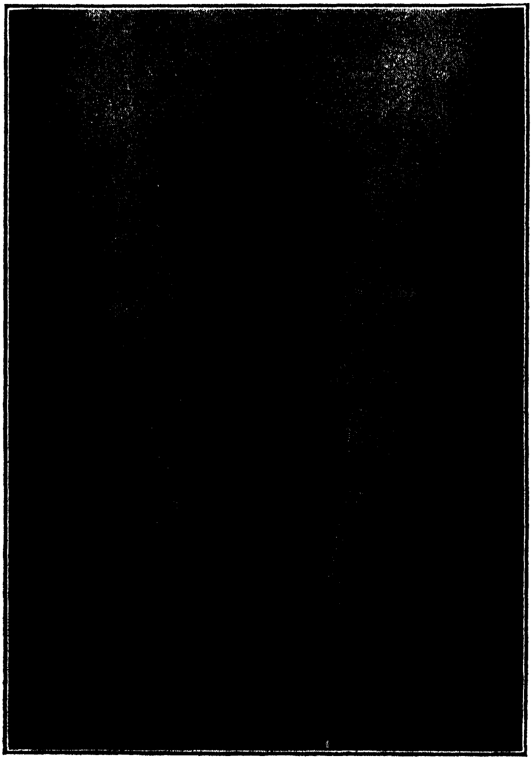


Fig. 89.—X-ray photograph of the legs of an infant with scurvy. Notice the increased density (whiteness) and the widening of the ends of the long bones. What is the cause of scurvy? (From Meakins: The Practice of Medicine.)

Severe ascorbic acid deficiency in man or guinea pigs (other animals apparently can synthesize the compound) causes *scurvy.* In this disease the gums are soft and boggy, and bleed easily.

Structural changes occur in the dentine of the teeth. Capillary bleeding, widening of the ends of the long bones, decalcification of bones, joint pains, and anemia are other symptoms. Children with the disease cease to grow.

The symptoms of mild ascorbic acid deficiency include a slow growth rate, some capillary bleeding, and possibly a decreased resistance to infections.

One international unit of the vitamin is equivalent to 0.05 mg. of pure ascorbic acid. The daily requirement of adults is estimated to be about 75 mg. The requirement is higher during pregnancy and lactation (100 to 150 mg.). The daily ration of children should contain from 30 to 75 mg. of ascorbic acid.

Drying, aging, and storing foods cause a loss of ascorbic acid activity. The vitamin readily is destroyed by prolonged boiling in contact with air. Its destruction is hastened by sodium bicarbonate and by the use of copper cooking utensils. Since it is water soluble, appreciable quantities may be lost in the cooking water.

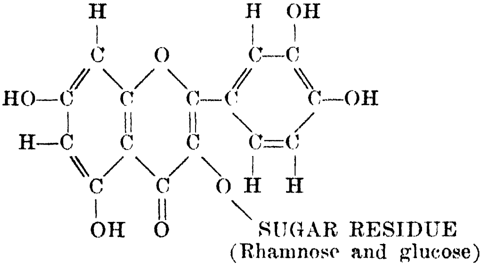
Citrus fruit, parsley, green peppers, potatoes, spinach, tomatoes, cantaloupe, cabbage, and turnips are excellent food sources.

Citrin

It has been claimed that citrus fruits and red peppers contain a substance other than ascorbic acid that is necessary for the prevention of capillary bleeding. This substance, which has been called *citrin,* or *vitamin P,* has been stated to be a mixture of the two plant pigments, hesperidin and eriodictyol glucoside. It has been claimed also that crystals of the material are composed entirely of hesperidin glucoside and a related substance with which it is in chemical equilibrium.

Many biochemists feel that the evidence for the existence of citrin as a vitamin is inconclusive. On the other hand, a number of clinical reports indicate that the substance is useful in the treatment of certain diseases accompanied by capillary bleeding. It has been suggested that perhaps citrin should be regarded as a drug rather than as a vitamin.

Rutin is a glucoside that occurs in many plants. The richest sources appear to be certain types of tobacco and buckwheat. Indeed, properly dried buckwheat may contain as much as several per cent of the compound. Preliminary evidence indicates that rutin may have the properties ascribed to citrin, and in fact some scientists are inclined to believe that some of the preparations of citrin described in the literature may have contained small amounts of rutin. Some clinicians have reported that the administration of the compound to selected patients with hypertension (high blood pressure) will decrease the incidence of hemorrhages such as brain hemorrhage ("stroke") and retinal hemorrhage. The exact role of rutin as a therapeutic agent and its relationship, if any, to citrin can be clarified only by future experimentation.



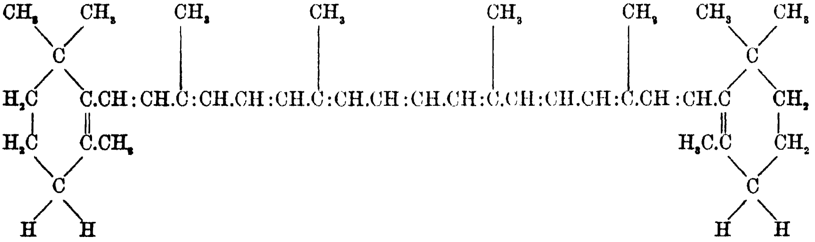
Rutin

THE FAT-SOLUBLE VITAMINS

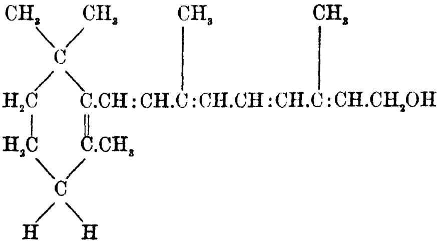
Vitamin A

Certain yellow pigments (carotenes, cryptoxanthin) found in plants can be converted to vitamin A in the animal body. The most important of these is β-carotene. One molecule of β-carotene can yield two molecules of vitamin A.

Two different forms of vitamin A (vitamin A_1 and vitamin A_2) are known to occur in nature. Vitamin A_1, the most abundant of these, has been isolated in crystalline form. When pure it is a crystalline solid, which is soluble in fats and organic solvents, but not in water. An isomer of vitamin A, known as neovitamin A, and having the same biological activity as A_1, is present in some fish-liver oils. All forms of vitamin A are alcohols, and they occur chiefly in the form of esters of fatty acids.



β-Carotene



Vitamin A_1

Vitamin A is absorbed from the intestinal tract more rapidly than are the carotenes. Bile is not necessary for the absorption of the vitamin, but is required for the absorption of the carotenes. Mineral oil, a common laxative, has been shown to inhibit carotene absorption. Most of the stored vitamin A of the body is present in the liver.

When vitamin A is omitted from the diet, the following important deficiency symptoms appear:

1. *A failure of growth.*

2. *A decrease in size and hardening (keratinization) of the cells of certain tissues (epithelial tissues) of the body.* These tissues include the lacrimal glands (which make the tears), the conjunctiva (membrane that lines the eyelids and covers the front of the eyeball), the cornea (transparent portion of the

eyeball), the salivary glands, the respiratory tract, the digestive tract, the genitourinary tract, the skin, and some of the ductless glands.

The failure of tear secretion and the keratinization of the cells of the cornea make it possible for bacteria to set up an infection of the eye. As a result, the cornea becomes cloudy and hardened. This condition, which may lead to permanent blindness, is called *xerophthalmia.*

The changes in the respiratory tract explain why people suffering from vitamin A deficiency are more likely to have colds, sinus disease, pneumonia, and other diseases of this system. It is not true, however, that colds can be prevented by taking vitamin A.

In animals, at least, the changes in the genitourinary tract may lead to sterility. In some cases, kidney stones accompany the deficiency.

In severe human deficiency the skin becomes rough and dry, and has a "tanned" appearance. Many of the sweat glands in the roughened areas are destroyed, and a skin rash usually develops. This skin condition has been called *phrynoderma.*

3. *Night blindness (nyctalopia).* The cells of the eye that are stimulated by light are called the rods and the cones. These cells are present in the retina, or inner lining of the eyeball. The cones respond chiefly to colored light, and are essential for normal color vision. The rods are stimulated by dim light. They contain a pigment known as *visual purple,* or *rhodopsin.* Visual purple appears to be a conjugated protein, in which vitamin A, or a pigment derived from vitamin A, is the prosthetic (nonprotein) group. In vitamin A deficiency visual purple cannot be made by the retina in normal quantities, and night blindness (inability to see in a dim light) develops.

4. *Defective tooth formation.* The formation of enamel is defective in vitamin A deficiency, and abnormalities also may occur in the dentine. This sometimes causes striking deformities of the teeth of young animals and human beings existing on a deficient diet.

One international unit of vitamin A is equivalent in activity to 0.0006 mg. of crystalline β-carotene. Adults probably require about 5,000 units (3 mg.) daily. The daily requirement of infants and children is somewhat lower (1,500 to 5,000 units). During pregnancy and lactation (milk secretion) the requirement is higher (6,000 to 8,000 units daily).

Fish-liver oils are the richest natural sources of vitamin A. Green plants, yellow vegetables, eggs, milk, and dairy products are excellent food sources.

Dried foods do not contain as much vitamin A as the food in fresh form. Prolonged cooking of food at temperatures above 100° C. also may cause some destruction of the vitamin.

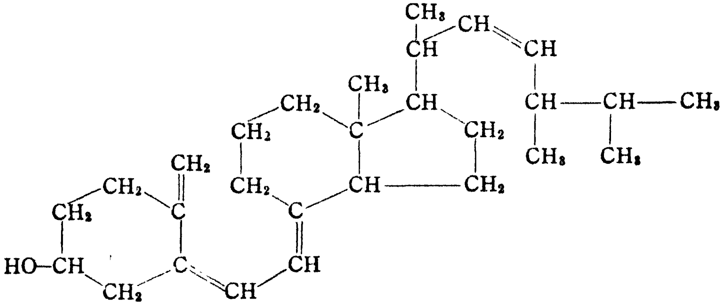
Vitamin D

A number of different compounds that have vitamin D activity are known. Most of these are "activated" forms of sterols, and can be prepared by exposing the appropriate sterol to ultraviolet radiant energy. The two most important forms are activated ergosterol (calciferol, vitamin D_2) and activated 7-dehydrocholesterol (vitamin D_3). Viosterol, a mixture of substances formed when ergosterol is irradiated with ultraviolet radiant energy, contains calciferol. Fish-liver oils contain activated 7-dehydrocholesterol, and this same substance is thought to be formed in the skin when the body is exposed to sunlight or to ultraviolet rays.

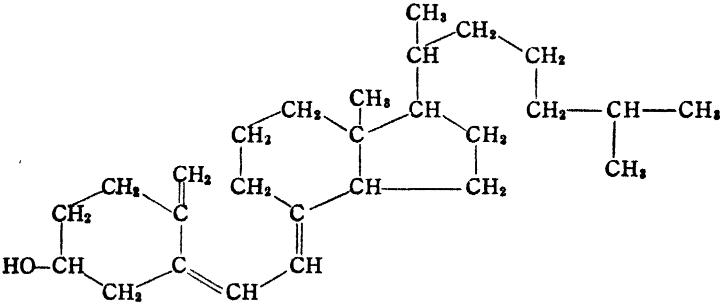
All forms of vitamin D are soluble in fats and fat solvents, but are insoluble in water. They are fairly stable to heat, alkalies, acids, and oxidation.

It appears to be the function of vitamin D to increase the absorption of calcium and phosphate from the intestinal tract. If the vitamin is omitted from the diet of young animals or children, symptoms characteristic of calcium or phosphate deficiency result.

Rickets is the disease caused by diets deficient in vitamin D and phosphate. Between the end (epiphysis) and shaft (diaphysis) of the bones of growing animals and children is a zone of cartilage, the *epiphyseal line.* In rickets the epiphyseal line continues to grow, but it is not converted to bone. This causes enlargements of many joints of the body. Bone development in general also is impaired, and the bones of a rachitic child are soft and easily deformed. The level of inorganic phosphate in the plasma is lower than normal. The child with rickets is irritable and does not grow at the usual rate. Mental development may be retarded. Rickets rarely occurs in older children or adults.



Activated ergosterol (Calciferol, Vitamin D_2)



Activated 7-dehydrocholesterol (Vitamin D_3)

Diets deficient in calcium and vitamin D cause *osteoporosis.* This condition is characterized by extensive decalcification (softening) of bones. The knobby joints characteristic of rickets do not appear, because the epiphyseal line ceases to grow when the diet is grossly deficient in calcium. Tetany (see page 691) may appear if the level of plasma calcium falls below normal.

Vitamin D deficiency causes a failure of proper formation of the dentine of the teeth. If the deficiency is severe, enamel formation also is impaired.

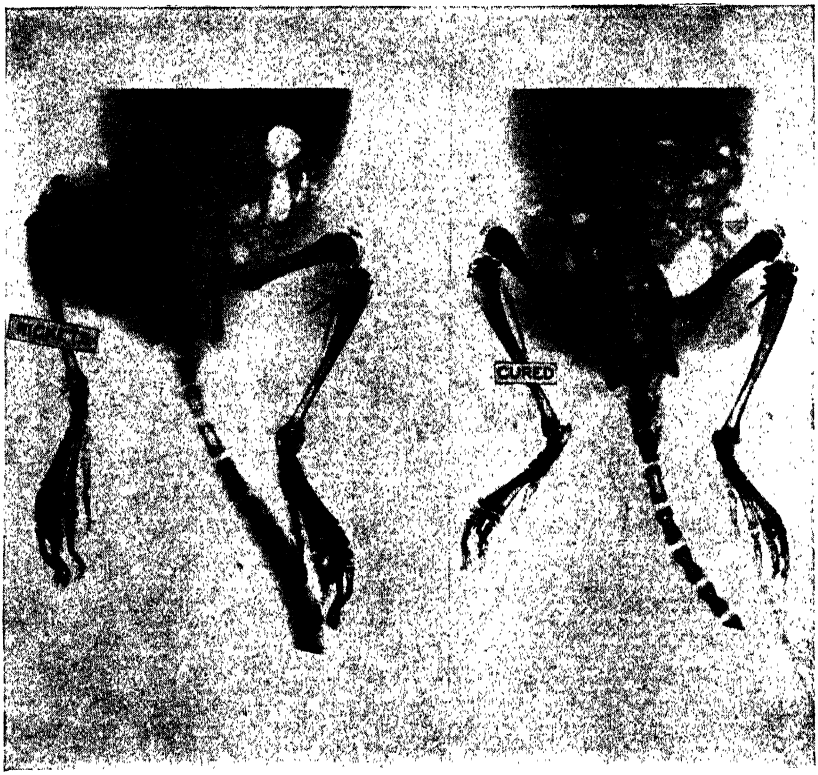


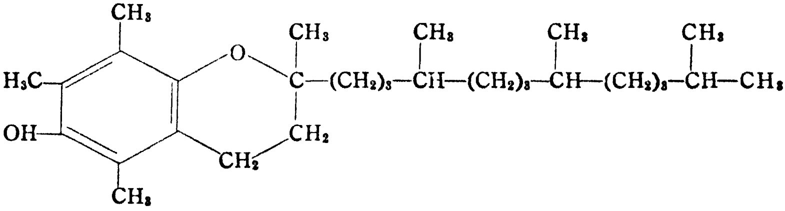
Fig. 90.—X-ray photograph of a rat with rickets produced by feeding a diet high in calcium, but low in phosphorus and vitamin D. The other photograph shows the rat after treatment with vitamin D. How does sunshine help prevent rickets? (Courtesy of Mead, Johnson & Co.)

An international unit of vitamin D has the same activity as 0.000025 mg. of crystalline calciferol. The daily requirement of the vitamin for adults is unknown, and, indeed, there is no good evidence that the majority of adults require it. If 400 to 800 units (0.01 to 0.02 mg.) are taken each day by the mother during pregnancy and lactation, it is believed that the requirement of the fetus or infant will be met. Infants and children probably require about 400 to 800 units daily.

Fish-liver oils, egg yolk, herring, foods irradiated with ultraviolet radiant energy, salmon, and sardines are excellent food sources. Exposure of the body to sunlight or to ultraviolet rays causes a formation of vitamin D in the skin.

Vitamin E

Several forms of vitamin E are known to occur in nature. The most active of these has been named *α-tocopherol (tokos* means childbirth; *pher* means to bear; and *ol* indicates that the compound is an alcohol). α-Tocopherol is a colorless or slightly yellow, odorless oil. It is a strong enough reducing agent to reduce alcoholic silver nitrate.



α-Tocopherol

When rats are placed on a diet deficient in vitamin E, the most striking symptom is sterility. In the case of the male animals, this sterility is due to a degeneration of the cells that make the male sex cells (spermatozoa). If this degeneration is allowed to proceed for too long a time, the condition cannot be cured by giving the vitamin. In the case of females, the sterility is due to the fact that the embryonic blood vessels fail to develop normally, and the unborn animal dies in the uterus. The lack of the vitamin has no effect on ovulation, fertilization, or initial formation of the placenta. The sterility of deficient females can be overcome by administration of vitamin E.

The most striking feature of vitamin E deficiency in laboratory animals other than the rat is paralysis; and, indeed, rats also may develop paralysis when they are kept on tocopherol-deficient diets. Creatine appears in the urine of the paralyzed animals.

Vitamin E is an excellent antioxidant, and can protect fats and fatlike substances from undergoing destructive oxidation. For example, vitamin A is more potent if given together with vitamin E, since less of the vitamin A is destroyed by oxidation in the intestinal tract and tissues of the body.

Vitamin E has been used clinically in the treatment of certain types of human sterility and paralysis. However, the results thus far obtained have been inconclusive, and it is not certain that this food factor is required by the human being.

An international unit of vitamin E is defined as the activity of 1.0 mg. of pure, synthetic, racemic α-tocopherol.

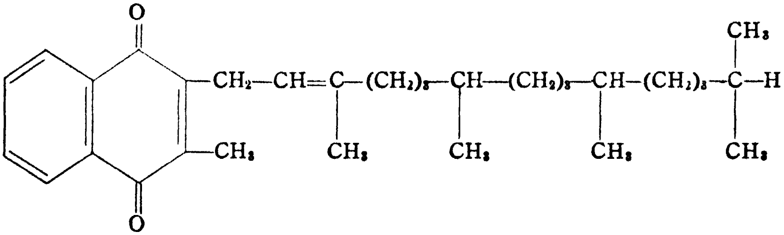
Vegetable oils (especially wheat germ oil), green leaves, whole grains, meat, milk, and eggs are good sources of the vitamin.

Vitamin K

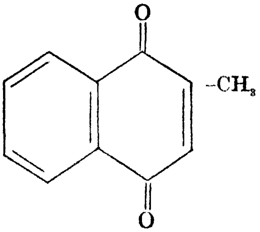
A number of substances possess vitamin K activity. The two forms of the vitamin known to occur in nature are termed vitamin K_1 and vitamin K_2. The most active synthetic vitamin is 2-methyl-1,4-naphthoquinone. Vitamin K_1 is a light yellow oil, crystallizing at low temperatures. Vitamin K_2 is a light yellow, crystalline compound, melting at 50°-52° C. The natural forms of the vitamin are soluble in fats and fat solvents, but are insoluble in water. However, several water-soluble substances that have vitamin K activity have been prepared in the chemical laboratory.

Vitamin K is necessary for the formation of prothrombin by the liver. It will be recalled that this is one of the plasma proteins, and that it is required for normal blood coagulation (see page 653). The principal sign of deficiency is the appearance of numerous capillary hemorrhages (bleeding areas) following slight injuries. The amount of prothrombin in the blood of deficient animals (usually chicks are used) is greatly reduced.

Vitamin K cannot be absorbed from the digestive tract in the absence of bile. In human adults vitamin K deficiency is most common when the person is suffering from some condition in which bile does not reach the doudenum in adequate amounts (obstructive jaundice, biliary fistula, and so on). It is dangerous to perform an operation on these persons unless the coagulation time of the blood is brought to normal by the administration of vitamin K (and bile salts if a water-insoluble form of the vitamin is given by mouth) prior to surgery. If the liver is severely diseased, the administration of the vitamin may be without beneficial effect, for the damaged liver may be unable to manufacture prothrombin.



Vitamin K_1



2-Methyl-1,4-naphthoquinone (menadione)

Some infants are born with subnormal blood levels of prothrombin. Such infants bleed readily, and may die because of brain hemorrhages (bleeding). In some cases, this condition can be prevented by giving the vitamin to the mother before delivery. Administration of the vitamin to the deficient infant rapidly restores the prothrombin level of the blood to normal.

Cabbage, alfalfa, liver, egg yolk, spinach, tomatoes, and cauliflower are good sources of vitamin K_1. Vitamin K_2 apparently is made in the intestinal tract by bacteria. It is present also in putrefying fish meal.

Vaccenic Acid

It has been reported that rats fed diets containing all known nutritional essentials grew better when they were fed summer butter than they did when fed winter butter or rapeseed oil. The enhancement of growth appeared to be due to the presence of vaccenic acid, an isomer of oleic acid (see page 271), in the summer butter.

$$CH_3(CH_2)_6CH{=}CH(CH_2)_8COOH$$

Vaccenic acid

Study Questions

1. What was the origin of the term vitamin?
2. Make up a definition for vitamin.
3. List the water-soluble vitamins known to be required by human beings.
4. What is meant by the phrase ''vitamin B complex''?
5. What was the first water-soluble factor to be recognized?
6. List the important symptoms of thiamine deficiency.
7. Can large amounts of thiamine be stored in the tissues? Give a reason for your answer.
8. What is cocarboxylase? What is its function?
9. What is an international unit of thiamine?
10. What are the daily requirements of thiamine for human beings?
11. List several good food sources of thiamine.
12. Is thiamine readily destroyed by cooking procedures?
13. What color is crystalline riboflavin?
14. What are the hydrolytic products of riboflavin?
15. What are the symptoms of riboflavin deficiency?
16. What role does riboflavin play in the transport of hydrogen from food molecules to molecular oxygen in the tissues?
17. What is the daily riboflavin requirement of the human being? What is a Bourquin-Sherman unit?
18. List several good food sources of riboflavin.
19. Give the chemical formula for nicotinic acid.
20. How does nicotinamide differ from nicotinic acid?
21. What is the role of nicotinamide in the transport of hydrogen from food molecules to molecular oxygen in the tissues?
22. What is the average normal level of nicotinamide in blood? What percentage of the total blood nicotinic acid is present in the red blood cells?
23. Name an excretory product of nicotinic acid metabolism.
24. List the symptoms of nicotinic acid deficiency in the human being. What name is given to this deficiency disease? What is blacktongue?

25. List several good food sources of nicotinic acid.
26. List the important deficiency symptoms of each of the following: pyridoxine, pantothenic acid, choline, biotin, inositol, *p*-aminobenzoic acid.
27. What is the principal result of pteroylglutamic acid deficiency?
28. What is the formula for ascorbic acid?
29. What are the probable functions of ascorbic acid in metabolism?
30. List the important symptoms of ascorbic acid deficiency.
31. What animals require ascorbic acid in their diets?
32. What is an international unit of ascorbic acid?
33. What are the estimated daily requirements of the human being for ascorbic acid?
34. Is ascorbic acid destroyed by cooking and drying procedures?
35. List several good food sources of ascorbic acid.
36. What is citrin? Rutin?
37. List the fat-soluble vitamins.
38. What is the most important provitamin of vitamin A?
39. How many forms of vitamin A are known to exist in nature?
40. Is bile required for the absorption of vitamin A or its provitamins?
41. What common laxative inhibits carotene absorption? How do you explain this?
42. In what organ is stored most of the reserve vitamin A of the body?
43. List the important effects caused by vitamin A deficiency.
44. Why does vitamin A deficiency cause night blindness?
45. What is phrynoderma?
46. What is an international unit of vitamin A?
47. What are the estimated daily requirements of vitamin A for the human being?
48. List some good sources of vitamin A.
49. Give the names of the two most important forms of vitamin D.
50. What is thought to be the chief function of vitamin D in metabolism?
51. List the important vitamin D deficiency symptoms.
52. What is an international unit of vitamin D?
53. What is the estimated daily human being requirement of vitamin D?
54. List some good sources of vitamin D.
55. Why is vitamin D sometimes referred to as the ''sunshine vitamin''?
56. What is the origin of the term tocopherol?
57. What name has been given to the most active form of vitamin E?
58. List the important symptoms of vitamin E deficiency.
59. Is vitamin E required by man? Give reasons for your answer.
60. List several good sources of vitamin E.
61. How does the appearance of pure vitamin K_1 differ from that of pure vitamin K_2?
62. What is the most active synthetic vitamin K?
63. What is the function of vitamin K?

64. What is the most important symptom of vitamin K deficiency?
65. Under what circumstances do human beings have symptoms of vitamin K deficiency?
66. Why may the administration of vitamin K to persons who have severe liver damage be ineffective in controlling capillary bleeding?
67. Why is vitamin K sometimes given to expectant mothers?
68. List several good sources of vitamin K.

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CHAPTER XXX

SUMMARY OF NUTRITIONAL REQUIREMENTS

Introduction.—It is the function of the diet to furnish the body with the various substances required for normal metabolism. Moreover, these substances must be supplied in adequate amounts. One group of essential dietary factors, the vitamins, already has been discussed. In this chapter the other factors known to be required for normal nutrition will be described briefly.

The Energy Requirement.—All the energy liberated by metabolic processes eventually is converted to heat. If, then, we could measure the total amount of heat lost by a person in a day, we could calculate his daily energy requirement in terms of large calories of food. (It will be recalled that the approximate energy value of 1 g. of protein is 4 large calories; of 1 g. of carbohydrate, 4 large calories; and of 1 g. of fat, 9 large calories.) Obviously, it is impractical to measure directly the total heat eliminated by a person in a day. However, it is possible to make fairly accurate calculations of energy requirements, provided we take into account the age, weight, height, sex, and type of occupation of the person whose requirement we wish to estimate.

The Basal Requirement.—The energy production (i.e., heat loss) when the body is at rest, when no digestion is going on, and when the body temperature is normal (37° C. or 98.6° F.) is called the *basal metabolism*. Basal metabolism represents, as nearly as we can measure it, the minimal amount of energy required for existence at a normal body temperature. It has been found experimentally that normal persons of the same age and sex eliminate, under basal conditions, approximately the same amount of heat each hour *per square meter of body surface*. Notice that heat loss is not correlated with body weight, but with *body surface area*. The number of large calories eliminated from each square meter of body surface in one hour under basal conditions is called the *basal metabolic rate*. This rate can be determined most conveniently by measuring with a special apparatus the amount of oxygen used during a measured time interval by a person under basal conditions. Under these conditions it is assumed that each liter of oxygen (measured at 760 mm. Hg pressure and 0° C.) consumed is equivalent to 4.78 large calories of energy. In actual practice the required average basal metabolic rate can be obtained by consulting a table of normal values (see Table XVI).

TABLE XVI

THE BOOTHBY AND SANDIFORD NORMAL STANDARDS

CALORIES PER SQUARE METER PER HOUR					
AGE	MALES	FEMALES	AGE	MALES	FEMALES
5	(53.0)	(51.6)	20-24	41.0	36.9
6	52.7	50.7	25-29	40.3	36.6
7	52.0	50.7			
8	51.2	48.1	30-34	39.8	36.2
9	50.4	46.9	35-39	39.2	35.8
10	49.5	45.8	40-44	38.3	35.3
11	48.6	44.6	45-49	37.8	35.0
12	47.8	43.4			
13	47.1	42.0	50-54	37.2	34.5
14	46.2	41.0	55-59	36.6	34.1
15	45.3	39.6	60-64	36.0	33.8
16	44.7	38.5	65-69	35.3	33.4
17	43.7	37.4			
18	42.9	37.3	70-74	(34.8)	(32.8)
19	42.1	37.2	75-79	(34.2)	(32.3)

Specific Dynamic Action of Food.—Foods have a stimulating effect on metabolism. Suppose the average basal requirement of a person is 2,000 large calories daily. If we keep this person at absolute rest in a fasting condition for twenty-four hours, the amount of heat eliminated will be 2,000 large calories. However, if we keep him at rest, but give him 2,000 large calories (his basal requirement) in the form of food during the twenty-four-hour period, we shall find that he eliminates now about 2,200 large calories of energy. In other words, metabolizing the food given him has resulted in the production of an extra 200 large calories of heat. The extra energy appears to be liberated almost entirely in the liver, and, therefore, cannot be used to do muscular work. This effect of food in stimulating metabolism is called *specific dynamic action.*

The specific dynamic action of protein is about 30 per cent; that is, there is an extra heat production of 30 large calories for

DUBOIS BODY SURFACE CHART

(As prepared by Boothby and Sandiford of the Mayo Clinic)

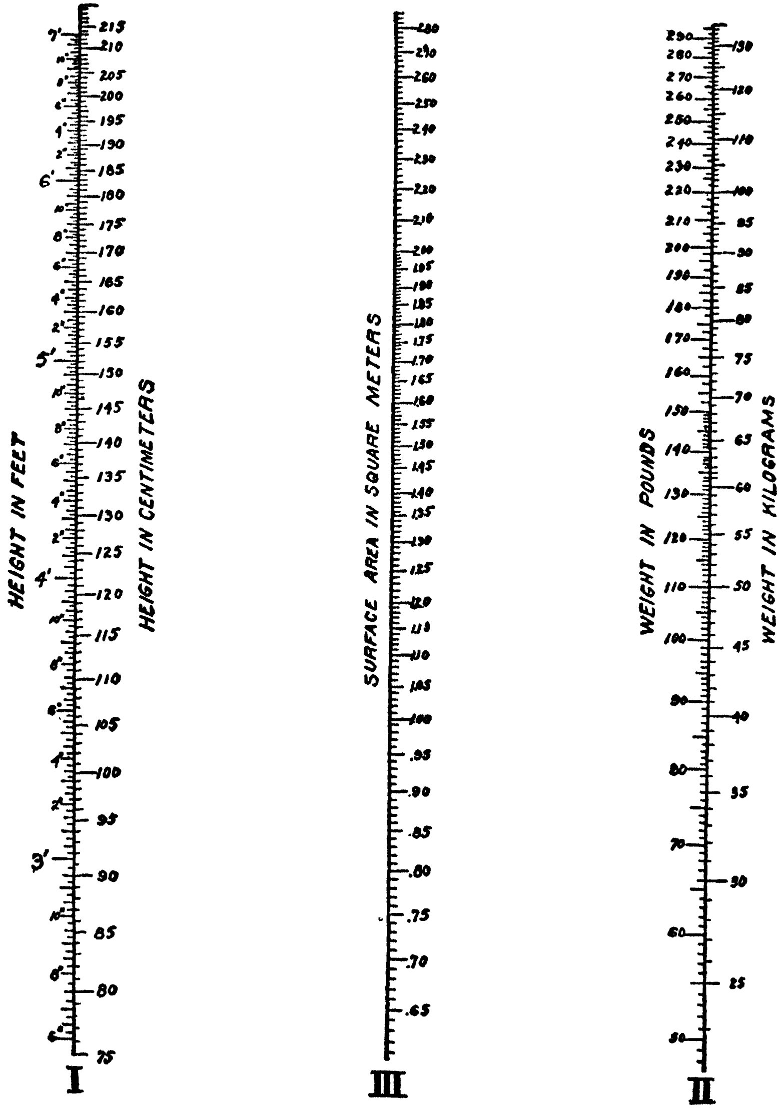

Fig. 91.—Body surface chart. Connect the correct height (column I) with the correct weight (column II) by means of a straight edge. The intersection of the straight edge with column II gives the surface area. What is your surface area?

each 100 large calories of food protein metabolized. The specific dynamic action of carbohydrate is about 5 to 6 per cent; and for fat, about 4 per cent.

Calculation of the Daily Energy Requirement.—Suppose we wish to calculate the daily energy requirement of a young lady 21 years of age. We shall assume that she is 64 inches tall and weighs 120 pounds. From Table XVI we learn that her normal basal metabolic rate is 36.9 large calories per square meter per hour. Fig. 91 tells us that her body surface area is 1.56 square meters. Therefore, her basal energy requirement for twenty-four hours will be:

$$36.9 \times 1.56 \times 24 = 1{,}382 \text{ large calories}$$

To this figure should be added about 10 per cent of the basal requirement (i.e., 138 large calories) to allow for specific dynamic action.

$$1{,}382 + 138 = 1{,}520 \text{ large calories}$$

Finally, the requirement for muscular work must be added. This requirement is quite variable, since it depends on the amount of physical work expended each day by the person. For people engaged in sedentary occupations (office workers, students, physicians, dentists, lawyers, dietitians, nurses, social workers, housewives, etc.) it varies usually between 500 and 1,000 large calories daily. On the other hand, lumbermen may require 4,000 large calories or more for muscular activity daily. Assuming that the young lady of our example is a college student, and is fairly active, we may suppose that her muscular work requirement is 700 large calories daily. Her total daily energy requirement thus will be:

$$1{,}520 + 700 = 2{,}200 \text{ large calories}$$

In proportion to body weight the energy requirement is higher in infancy and childhood than in adult life (see Tables XVI and XVII). This is due partly to the fact that the basal metabolism is higher, and partly to the fact that energy (food) is required for growth.

TABLE XVII

AVERAGE DAILY ENERGY REQUIREMENT PER KILOGRAM OF BODY WEIGHT

AGE	LARGE CALORIES PER KILOGRAM
1 year	100
2 years	90
5 years	80
9 years	70
13 years	65
17 years	50
Adult, no exercise	33
Adult, light exercise	37
Adult, moderate exercise	43
Adult, hard labor	48

The Protein Requirement.—Amino acids are required for the synthesis of body protein, enzymes, pigments, hormones, and the other nitrogenous substances of the body. If extra protein is ingested, a portion of it may be used to form glycogen (and perhaps fat), or the extra amino acids may be oxidized with the production of carbon dioxide, water, urea, and energy.

Certain amino acids present in food proteins cannot be synthesized in the body, and must be present in the diet. In their absence, young animals cease to grow, and adult animals lose weight. If the amino acid deficiency is continued for too long a time, death of the animal occurs. The *essential amino acids* are threonine, valine, leucine, isoleucine, methionine, lysine, tryptophan, histidine, and phenylalanine (see page 557). Arginine also is required for a *normal* rate of growth. In the studies that led to the discovery of the essential amino acids, rats and dogs were used as test animals. However, it is assumed that these same amino acids are required by man, although the evidence is not conclusive in the case of histidine and arginine.

Proteins that contain adequate amounts of the essential amino acids are said to be *adequate proteins.* Eggs, kidneys, milk, and liver are the best food sources of adequate proteins. The proteins of lean meat, fish, poultry, shellfish, potatoes, and soybeans are nearly as good from a nutritional point of view as those just mentioned. In general, plant proteins, such as those in nuts, legumes, cereals, and most vegetables, are of poor nutritional quality; or, at best, are only fair. It often happens, however, that two or more proteins, each of poor quality, supply all the essential amino acids when they are eaten together.

The amount of protein that should be present in adult diets is estimated to be about 70 g. daily. This is slightly more than 1 g. per kilogram of body weight. Infants should receive from 2 to 2.5 g. per kilogram daily if the source is breast milk, or from 3 to 3.5 g. per kilogram daily if cow's milk is used. Growing children probably require each day from 2 to 2.5 g. of protein per kilogram of body weight.

Adults existing on adequate diets are in nitrogen equilibrium, or nitrogen balance; that is, the amount of nitrogen lost from the body each day is equal to the nitrogen ingested in the food. Growing infants and children, or persons convalescing from wasting diseases, are in positive nitrogen balance: the nitrogen intake exceeds the nitrogen excretion. This is due to the fact that a portion of the ingested protein is utilized in building new tissue. When the dietary protein is of poor nutritional quality, or is not ingested in adequate amounts, a negative balance results, and more nitrogen is lost in the excreta than is taken into the body with the food.

Ordinarily, from 10 to 20 per cent of the caloric intake is furnished by protein.

The Lipid Requirement.—When rats are placed on a lipid-free diet, they cease to grow, fail to bear young, and develop a characteristic skin disorder. After a time, blood appears in the urine, and the animals soon die. It has been found that the addition of any of certain unsaturated fatty acids to the diet will prevent this deficiency syndrome. These *essential fatty acids* (see page 271) are linoleic acid (2 double bonds per molecule), linolenic acid (3 double bonds per molecule), and arachidonic acid (4 double bonds per molecule). Other evidence indicates also that the body can make saturated fatty acids and fatty acids whose molecules contain one double bond, but is unable to synthesize more unsaturated fatty acids.

At present we are not certain that human beings require the essential fatty acids. It appears to be true, however, that certain types of eczema (a skin disorder) can be cured or alleviated by the administration of unsaturated fats, such as raw linseed oil or corn oil. The blood plasma of patients who respond to this therapy contains less than the average normal amount of unsaturated fatty acids.

Following the first World War, it was reported that diets low in lipid resulted in early fatigue of the soldiers. It is known today that the thiamine requirement is elevated when fat is not present in adequate amounts in the diet. It is possible, but certainly not proved, that this tendency to develop early fatigue on low fat diets might be prevented by increasing the thiamine intake.

Most of the choline of the diet is present in the phospholipid fraction of the food (see page 285).

Ordinarily, from 25 to 35 per cent of the calories of the diet is supplied by lipid.

Dietary Carbohydrate.—Theoretically, carbohydrate is not a dietary essential, for it can be made in the body from protein and from the glycerol present in lipids. Practically, however, it is the major energy food of the diet. Diets containing chiefly protein and fat are not palatable to many people, and in any case are much too expensive for the average person to afford. Usually, from 45 to 65 per cent of the caloric value of the diet is supplied by digestible carbohydrate.

Plant foods (fruits and vegetables) contain fairly high percentages of undigestible carbohydrate (cellulose and hemicellulose). Most persons require a certain amount of this type of carbohydrate for the prevention of constipation (see page 607). Undigestible carbohydrate is listed as "crude fiber" in most nutritional charts.

The Inorganic Requirement.—In addition to water, a number of inorganic substances are known to be essential for normal nutrition. The metabolic roles of the most important of these substances have been discussed in Chapter XXVII. The average amounts of them required each day by children and by adults are listed in Table XIX.

The daily water intake for adults is about 35 to 45 cc. per kilogram (16 to 22 cc. per pound) of body weight. The requirement is higher in infancy and childhood. For example, nursing infants receive from 125 to 150 cc. of water per kilogram of body

TABLE XVIII

SCHEMATIC ADAPTATION OF SUGGESTED DIETS FOR CHILDREN, SHOWING METHODS OF ADDITION TO A BASIC DIET*
Graded Additions (Each Added to Previous Total)

BASIC FOR AGE: PROTECTIVE FOODS	9 MO.-1 YR.		1-2 YR.		2-3 YR.		3-4 YR.		4-5 YR.		5-7 YR.		TOTAL ACCUMULATION		7-10 YR.		12-14 YR.	
	AMT.	CAL.	AMT.	CAL.	AMT.	CAL.	AMT.	CAL.	AMT.	CAL.	AMT.	CAL.			AMT.	CAL.	TOTAL AMOUNTS	CAL.
Milk (including cheese)	3 cups	498							½ cup	83	½ cup	83	4 cups	664			4 cups	664
Egg	1	74											1	74	½-1	35- 74	1-2	74-150
Lean meat, fish, Poultry	⅕-¼ cup	50				50							½ cup	100		50-100	3 servings lean (beef, chicken, etc.) or 2 servings medium fat (pork, salmon)	400-600

Fruit and vegetables:									
Orange	1 medium 45						1 45		1 medium 45
High calorie fruit (½ banana, ⅓ cup apricots, 3 prunes, peaches, etc.)	90		45		45	45	2½ servings 225		2½-3 servings 225-270
High calorie vegetable (potato, peas, soy or Lima Beans)	⅓-½ cup 80		20	30		50	2 servings 180	¼-½ cup 50-100	2-3 servings 160-240
Low calorie vegetables (tomato, greens, string beans, etc.)	2 servings of ¼-⅛ cup 20					10	2 servings 30		2-3 servings 30- 45
Cod-liver oil	1 tsp. 30				30	75	1 tsp.-1 tbsp. 235	75	1 tsp.-1 tbsp. 30-100
Butter	½ tbsp. 50	½ tbsp. 50					1½-2 tbsp.		2-4 tbsp. 200-400
Supplementary energy foods									
Whole cereals,									
Breakfast cereal	½ cup 70						½ cup 70		1 cup 140
Bread { Including rice, macaroni, cake, crackers, cookies, etc.		1 slice 75				1 slice 75	2 slices 150	1 slice 75	3-4 slices 215-460
Sugar								1 tbsp. 50	2 tbsp. 100
Total	1,007	1,132	1,247	1,277	1,435	1,773	1,773	1,906-2,245	2,428-2,814

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*Compiled 1937. The individual child may vary from 100 calories in the younger ages to 300-400 in the older. Do not permit the supplementary energy foods to substitute for the protective foods in fulfilling caloric requirement.

TABLE XIX

THE DAILY REQUIREMENT OF SOME INORGANIC SUBSTANCES

	CHILDREN (45 POUNDS)	ADULTS (150 POUNDS)
Sodium chloride	1.65 g.	10.0 g.
Potassium	1.5 g.	3.0 g.
Phosphorus	1.0 g.	1.3 g.
Calcium	1.0 g.	0.8 g.
Magnesium	0.25 g.	0.35 g.
Iron	8.0 mg.	12.0 mg.
Copper	1.0 mg.	1.5 mg.
Manganese	3.0 mg.	1.5 mg.
Iodine	0.15 mg.	0.1 mg.
Zinc	--------	Trace
Cobalt	--------	Trace
Sulfur	Intake will be adequate if the protein intake is adequate	

weight daily. Approximately two-thirds the water taken into the body is present in solid and semisolid food; the other third is ingested in liquid form.

Acid and Alkaline Effects of Food.—Certain foods of the diet yield acid end products when they are catabolized in the tissues. Most acid-forming foods contain high percentages of protein. (It will be remembered that acid sulfates, acid phosphates, and uric acid are among the excretory products derived from protein.) Certain fruits contain fairly large amounts of benzoïc acid. This acid is not metabolized in the tissues; instead, it is conjugated with glycine to form hippuric acid. Hippuric acid is eliminated in the urine. Typical acid-forming foods are meat, fish, poultry products, cereals, bread, cheese, corn, lentils, peanuts, pecans, walnuts, cranberries, plums, and prunes.

Most of the acid end products of metabolism are excreted in the urine in combination with alkaline metals (sodium, potassium, calcium, magnesium). If these metals are not furnished by the diet, they must be furnished by the tissues, with a resulting loss of base from the body (acidosis). Most of the metals in alkali-forming foods are present as organic salts. In the body the organic portion of the salt usually is oxidized to carbon dioxide and water. The metals that remain combine either with carbon dioxide and water to form bicarbonates, or with the end products derived from acid-forming foods. Most fruits and vegetables (with the exceptions mentioned above) are alkali-forming. Other alkali-forming foods are milk, mince meat, almonds, Brazil nuts, chestnuts, and coconut.

Study Questions

1. What is the function of the diet?
2. What is the caloric value of 1 g. of each of the following: protein, fat, carbohydrate, sodium chloride?
3. An average doughnut weighs 60 g. It contains 6.6 per cent protein, 52.5 per cent digestible carbohydrate, and 21 per cent fat. How many large calories of energy are supplied by one such doughnut?
4. Define basal metabolic rate. How can it be determined?
5. What is your normal basal metabolic rate?
6. What is meant by specific dynamic action of foods?
7. How much *extra* energy is produced by the metabolism of 10 g. of food protein? Of 10 g. of food carbohydrate? Of 10 g. of food fat?
8. In what organ of the body is the heat of specific dynamic action produced?
9. What is your body surface area in square meters?
10. Calculate your caloric requirement for one day.
11. Keep a record of your diet for one day. Using the tables given in the Appendix of this book, calculate the following:
    (a) Total caloric intake for the day.
    (b) Grams of protein, carbohydrate, and fat ingested.
    (c) Intake of vitamin A, thiamine, ascorbic acid, vitamin D, and riboflavin.
    (d) Intake of calcium, iron, copper, and phosphorus.
    (e) Intake of undigestible carbohydrate (crude fiber).
    (f) Excess of acid or alkaline end products in terms of cubic centimeters of 0.1 N acid or alkali.
12. At what age is the average daily caloric requirement per kilogram of body weight 100 large calories? At what age is it half this (50 large calories)?
13. Why is protein required in the diet?
14. Name the essential amino acids.
15. Define adequate protein. What foods are the best sources of adequate proteins?
16. How much protein should be present in the diet each day?
17. What is meant by nitrogen equilibrium? Under what circumstances is a person in positive nitrogen balance? In negative nitrogen balance?
18. What percentage of the caloric intake usually is furnished by protein?
19. What symptoms develop when rats are placed on a diet deficient in unsaturated fatty acids?

20. Name the essential fatty acids.
21. Is there any evidence that lipids are essential in the diet of human beings? Give reasons for your answer.
22. Is carbohydrate a dietary essential?
23. What percentage of the caloric intake is supplied by carbohydrate?
24. Why is it desirable for the diet to contain some undigestible carbohydrate?
25. List the amounts of the following substances required each day by children and by adults: sodium chloride, phosphorus, calcium, iron, copper, iodine. List some other inorganic substances necessary for normal nutrition.
26. Approximately how much water is ingested each day by a normal adult who weighs 154 lb.?
27. Is the water requirement in childhood higher or lower than in adult life? How do you explain this?
28. Name several acid-forming foods.
29. Lemons taste sour, indicating that they contain acids. However, they are listed as an alkali-forming food. How do you explain this?
30. Name several alkali-forming foods.
31. Most fruits are alkali-forming foods. How do you explain the fact that cranberries, plums, and prunes are listed as acid-forming foods?

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APPENDIX

INTERNATIONAL ATOMIC WEIGHTS, 1947

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	Symbol	Atomic Number	Atomic Weight
Aluminum	Al	13	26.97
Antimony	Sb	51	121.76
Argon	A	18	39.944
Arsenic	As	33	74.91
Barium	Ba	56	137.36
Beryllium	Be	4	9.02
Bismuth	Bi	83	209.00
Boron	B	5	10.82
Bromine	Br	35	79.916
Cadmium	Cd	48	112.41
Calcium	Ca	20	40.08
Carbon	C	6	12.010
Cerium	Ce	58	140.13
Cesium	Cs	55	132.91
Chlorine	Cl	17	35.457
Chromium	Cr	24	52.01
Cobalt	Co	27	58.94
Columbium	Cb	41	92.91
Copper	Cu	29	63.54
Dysprosium	Dy	66	162.46
Erbium	Er	68	167.2
Europium	Eu	63	152.0
Fluorine	F	9	19.00
Gadolinium	Gd	64	156.9
Gallium	Ga	31	69.72
Germanium	Ge	32	72.60
Gold	Au	79	197.2
Hafnium	Hf	72	178.6
Helium	He	2	4.003
Holmium	Ho	67	164.94
Hydrogen	H	1	1.0080
Indium	In	49	114.76
Iodine	I	53	126.92
Iridium	Ir	77	193.1
Iron	Fe	26	55.85
Krypton	Kr	36	83.7
Lanthanum	La	57	138.92
Lead	Pb	82	207.21
Lithium	Li	3	6.940
Lutecium	Lu	71	174.99
Magnesium	Mg	12	24.32
Manganese	Mn	25	54.93
Mercury	Hg	80	200.61
Molybdenum	Mo	42	95.95
Neodymium	Nd	60	144.27
Neon	Ne	10	20.183
Nickel	Ni	28	58.69
Nitrogen	N	7	14.008
Osmium	Os	76	190.2
Oxygen	O	8	16.0000
Palladium	Pd	46	106.7
Phosphorus	P	15	30.98
Platinum	Pt	78	195.23
Potassium	K	19	39.096
Praseodymium	Pr	59	140.92
Protactinium	Pa	91	231
Radium	Ra	88	226.05
Radon	Rn	86	222
Rhenium	Re	75	186.31
Rhodium	Rh	45	102.91
Rubidium	Rb	37	85.48
Ruthenium	Ru	44	101.7
Samarium	Sm	62	150.43
Scandium	Sc	21	45.10
Selenium	Se	34	78.96
Silicon	Si	14	28.06
Silver	Ag	47	107.880
Sodium	Na	11	22.997
Strontium	Sr	38	87.63
Sulfur	S	16	32.066
Tantalum	Ta	73	180.88
Tellurium	Te	52	127.61
Terbium	Tb	65	159.2
Thallium	Tl	81	204.39
Thorium	Th	90	232.12
Thulium	Tm	69	169.4
Tin	Sn	50	118.70
Titanium	Ti	22	47.90
Tungsten	W	74	183.92
Uranium	U	92	238.07
Vanadium	V	23	50.95
Xenon	Xe	54	131.3
Ytterbium	Yb	70	173.04
Yttrium	Y	39	88.92
Zinc	Zn	30	65.38
Zirconium	Zr	40	91.22

COMPOSITION OF
(EDIBLE
(Reprinted from *Nutritional Charts* through

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE OTHER THAN FIBER	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Artichokes (globe)	50	2.9	8.7	0.4	3.2	1.1	.031	.087	.00095	.00031
Asparagus	23	2.2	3.2	0.2	0.7	0.7	.021	.062	.00096	.00014
Bamboo shoots	30	2.5	4.3	0.3	0.8	0.8	.005	.040	.00070	.00029
Beans, baked	99	6.0	17.8	0.4	1.0	2.3	.052	.155	.00320	.00023
Beans, dried	334	22.0	58.2	1.5	3.9	3.9	.160	.471	.00950	.00069
Beans, green	37	2.4	6.3	0.2	1.4	0.8	.065	.044	.00098	.00010
Beans, dried lima	324	20.7	57.3	1.3	3.8	3.8	.072	.386	.00860	.00086
Beans, green lima	125	7.5	22.0	0.8	1.5	1.7	.063	.158	.00240	.00086
Beans, green kidney	88	5.7	15.5	0.4	0.9	1.5	.016	.052	.00057	.00065
Beans, soy, dried	426	40.0	25.9	18.0	3.5	4.6	.255	.611	.00600	.00160
Beans, soy, green	158	16.0	9.7	6.1	1.5	2.0	.072	.231	.00300	-----
Beans, soy, sprouts	66	7.6	6.7	1.0	0.9	---	.042	.054	.00250	-----
Beets	42	1.6	8.7	0.1	0.9	1.1	.029	.039	.00085	.00019
Beet greens	28	2.0	4.2	0.3	1.4	1.7	.094	.040	.00310	.00009
Broccoli	32	3.3	4.2	0.2	1.3	1.1	.114	.060	.00140	.00015
Brussels sprouts	53	4.4	7.6	0.5	1.3	1.3	.027	.121	.00120	.00010
Cabbage	25	1.4	4.3	0.2	1.0	0.8	.045	.029	.00043	.00005
Carrots	40	1.2	8.2	0.3	1.1	1.0	.056	.046	.00064	.00008
Cauliflower	27	2.4	4.0	0.2	0.9	0.9	.022	.072	.00094	.00014
Celeriac (celery root)	39	1.7	7.4	0.3	1.4	0.9	.047	.071	.00060	.00013
Celery	19	1.3	3.0	0.2	0.7	1.1	.078	.037	.00062	.00001
Chard, leaves	22	1.4	3.6	0.2	0.8	1.2	.105	.036	.00400	.00011
Chives	52	3.8	7.8	0.6	2.0	---	.048	.057	.00250	-----
Collards	45	3.9	6.0	0.6	1.2	1.7	.207	.075	.00170	-----
Corn, canned (yellow)	73	2.0	15.1	0.5	1.0	1.0	.004	.051	.00047	.00010
Corn, green (yellow)	104	3.7	19.7	1.2	0.8	0.7	.009	.120	.00047	.00006
Cucumbers	13	0.7	2.2	0.1	0.5	0.4	.016	.033	.00033	.00006
Dandelion greens	45	2.7	7.0	0.7	1.8	2.0	.187	.070	.00300	.00015
Eggplant	25	1.1	4.6	0.2	0.9	0.5	.011	.034	.00047	.00010

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[a] The data as given apply to the edible portion of food in the raw state and on the wet basis. When either home-cooked or canned, the values will usually be considerably lower than those given here, because of dilutions with cooking water, the discarding of cooking liquid containing soluble nutrients, and a variable but frequently large destruction of vitamins through heat or oxidation in the cooking process. Each plant food may vary in composition, in mineral content, and in vitamin value, depending upon such factors as variety, maturity, soil, climate, storage and method of preparation. The figures reported are averages and give an indication of the relative contribution of each product. The data are subject to change as more evidence becomes available.

[b] Expressed in ml. of normal reagent, per 100 grams or per 100 ml. of food.

VEGETABLES[a]

PORTION)

the courtesy of the H. J. Heinz Company.)

ALKALINE (+) OR ACID ( ) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A[c]	B_1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE[d]	WEIGHT IN GRAMS
+ 7.6	390	150	30	□	11	50	1 heart, edible leaf portion	100
+ 0.8	1,400	180	130	1	40	23	6 stalks	100
+ 8.0	22	54	x	0	6	30	¾ c.	100
+ 6.0	50	120	100	1	0	99	½ c.	100
+18.0	110	500	320	2	0	94	2 T. shelled	28
+ 5.4	1,200	95	150	1	23	37	1 c. stringless	100
+42.0	100	510	750	2	0	91	⅛ c. shelled	28
+28.0	900	340	200	1	42	125	⅔ c. shelled	100
+18.0	900	210	95	<1	28	88	⅔ c. shelled	100
+ 4.5	570	1200	750	2	0	119	3 T. shelled	28
+17.0	350	470	300	1	30	158	⅔ c. shelled	100
+16.0	170	100	120	1	14	66	1 c.	100
+11.0	50	50	70	<1	8	42	⅔ c.	100
+27.0	21,000	110	250	<1	50	28	1 c.	100
+ 9.3	9,000	130	250	1	80	32	1 c. ''curd''	100
+11.0	400	170	75	0	150	53	6	100
+ 6.0	38	80	66	0	100	14	¾ c. shredded as slaw	57
+11.0	12,000	70	65	<1	4	40	1 large, scraped	100
+ 5.3	70	100	130	<1	75	27	1 c. ''curd''	100
+ 8.8	□	□	□	□	□	39	¾ c. pared	100
+ 7.8	10	36	35	0	9	8	2 stalks	40
+16.0	9,000	200	140	0	40	22	1½ c.	100
+13.0	500	120	□	□	70	52	2 bunches	100
+	8,800	200	250	<1	70	45	⅔ c.	100
- 1.8	200	20	50	1	5	84	½ c.	115
- 2.0	390	150	140	1	12	104	½ c. cut from cob	100
+ 7.9	35	40	90	0	10	7	10 slices, pared	57
+18.0	12,000	200	220	<1	36	45	1 c.	100
+ 6.3	70	60	31	<1	10	25	2 slices, pared	100

[c] Vitamin A is expressed in International units, vitamins B_1 and B_2 in micrograms, and vitamin C and nicotinic acid in milligrams per 100 grams or per 100 ml. of food.

[d] The measure as given is based upon the edible portion only and upon articles of average size. The food is calculated as in the raw state. These figures are not offered as exact data but merely as a guide in estimating average portions or servings. The bones of meat and fish and skin of fowl are discarded along with most of the fat.

T. = tablespoon
t. = teaspoon
c. = cup
□ = data are lacking or insufficient
< = less than
0 = poor or none
x = fair
xx = good
xxx = excellent

COMPOSITION OF
(EDIBLE

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE OTHER THAN FIBER	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Endive	21	1.6	3.2	0.2	0.8	0.9	.104	.039	.00120	.00009
Escarole (chicory)	18	1.6	2.1	0.3	0.8	1.0	.027	.029	.00100	.00014
Garlic	95	4.4	19.0	0.2	1.0	1.2	.010	.143	.00230	.00036
Horseradish	91	3.2	19.0	0.2	2.4	1.8	.119	.070	.00200	.00014
Kale	45	3.9	6.0	0.6	1.2	1.7	.195	.060	.00250	.00052
Kohl-rabi	32	2.1	5.6	0.1	1.1	1.1	.195	.060	.00061	.00014
Lambsquarters	44	3.8	5.7	0.7	2.6	3.0	---	---	-----	----
Leeks	40	2.5	6.6	0.4	1.3	1.0	.058	.056	.00065	.00050
Lentils, dried	334	24.7	56.6	1.0	3.3	3.2	.102	.383	.00760	00066
Lettuce	16	1.2	2.3	0.2	0.6	0.9	.043	.023	.00070	.00004
Marrow, vegetable	17	0.5	3.4	0.1	0.6	0.4	.014	.013	.00022	.00003
Mushrooms	30	3.9	3.1	0.2	0.9	1.3	.014	.154	.00180	00180
Mustard greens	25	2.3	3.2	0.3	0.8	1.2	.220	.038	.00290	.00030
Okra	35	1.8	6.4	0.2	1.0	0.8	.082	.062	.00063	.00020
Onions	45	1.4	9.5	0.2	0.8	0.6	.034	.045	.00048	.00008
Parsley	53	3.7	7.2	1.0	1.8	2.4	.045	.029	.00320	.00021
Parsnips	75	1.5	16.0	0.5	2.2	1.2	.059	.076	.00077	.00012
Peas, dried	327	23.8	54.8	1 4	5.4	3.0	.084	.400	.00570	.00140
Peas, green	92	6.7	15.5	0.4	2.2	0.9	.028	.127	.00210	.00024
Peppers, green	24	1.2	4.3	0.2	1.4	0.5	.006	.026	.00040	.00010
Potatoes, sweet	121	1.8	26.9	0.7	1.0	1.1	.019	.045	.00077	.00015
Potatoes, white	84	2.0	18.7	0.1	0.4	1.0	.014	.058	.00091	.00017
Pumpkins	31	1.2	6.0	0.2	1.3	0.8	.023	.059	.00093	.00003
Radishes	20	1.2	3.5	0.1	0.7	1.0	.021	.029	.00083	.00016
Rhubarb	15	0.5	3.1	0.1	0.7	0.7	.044	.031	.00056	.00005
Rutabagas	36	1.1	7.6	0.1	1.3	0.8	.074	.056	.00036	.00015
Salsify (oyster plant)	78	3.5	13.7	1.0	1.8	0.9	.060	.053	.00160	.00029
Sauerkraut	14	1.1	2.0	0.2	1.4	2.4	.046	.031	.00040	.00004
Spinach	22	2.3	2.6	0.3	0.6	1.5	.067	.068	.00260	.00012
Squash, summer	17	0.6	3.4	0.1	0.5	0.4	.018	.015	.00035	.00008
Squash, winter	38	1.5	7.4	0.3	1.4	0.8	.019	.015	.00055	.00004
Taro	93	2.0	20.7	0.2	0.8	1.2	.039	.049	.00390	-----
Tomatoes	20	1.0	3.4	0.3	0.6	0.6	.011	.026	.00044	.00007
Turnips	30	1.1	6.0	0.2	1.1	0.7	.064	.046	.00052	.00009
Turnip greens	32	2.9	4.2	0.4	1.2	1.8	.216	.075	.00350	.00009
Water cress	21	1.7	2.8	0.3	0.5	1.1	.157	.046	.00300	.00004
Yams	103	2.1	23.3	0.2	0.8	1.0	.044	.050	.00110	.00001
Yautia, yellow	110	2.2	24.9	0.2	0.6	0.6	.023	.069	.00160	-----

See pages 750 and 751 for footnotes.

VEGETABLES
PORTION)

ALKALINE (+) OR ACID (−) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B₁	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE	WEIGHT IN GRAMS
+ 7.0	4,000	100	200	1	15	9	½ head	45
+ 4.0	23,000	75	210	<1	8	3	¼ head	16
----	0	150	4	□	14	--	1 clove, peeled	2
+ 4.8	□	70	□	□	90	9	1 t.	10
+ 7.7	11,000	190	500	<1	150	45	1 c. leaves	100
+ 8.0	2,500	50	75	0	65	32	½ c.	100
+	19,000	x	x	□	85	44	1 c. leaves	100
+ 7.0	1,000	150	x	□	24	23	2 stalks	57
-16.0	200	500	400	3	0	94	2 T.	28
+ 7.4	1,000	60	70	0	13	12	¼ head	75
+ 1.9	30	45	□	□	11	17	⅝ c.	100
+ 4.0	120	120	500	6	8	30	7	100
----	11,000	140	370	<1	180	25	1 c. leaves	100
+ 4.5	400	130	100	<1	30	17	5 pods	50
+ 1.5	50	33	60	0	20	23	1	50
+	5,000	80	300	□	140	--	1 sprig	1
+12.0	200	120	80	0	30	75	½ large, scraped	100
+ 5.0	5,100	870	300	3	0	92	2 T.	28
+ 1.3	2,000	390	150	1	25	92	¾ c. shelled	100
+ 1.7	5,000	70	100	0	180	24	1 empty pod	100
+ 6.7	4,200	140	70	1	33	175	1 pared	145
+ 7.0	40	150	50	1	28	101	1 pared	120
+ 1.5	2,500	50	45	<1	10	31	½ c. seeded, rind removed	100
+ 2.9	25	40	35	0	26	7	5	35
+ 8.5	100	24	30	0	15	15	1 c. stems	100
+ 8.5	25	75	100	<1	30	36	¾ c. scraped	
+ 2.9	□	□	□	□	7	78	2 scraped	100
+ 5.7	20	24	50	0	10	14	⅔ c.	100
+27.0	8,400	100	300	1	75	22	1 c. leaves	100
+ 1.0	1,000	42	52	1	23	17	1 c. seeded, rind removed	100
+ 2.6	7,000	48	46	1	18	38	1 c. seeded, rind removed	100
+18.0	60	90	xx	□	10	93	1 corm, pared	100
+ 5.6	2,000	80	60	<1	27	20	1 small, cored	100
+ 2.7	15	60	50	<1	43	30	¾ c. pared	100
+ 2.3	16,000	140	370	1	120	32	1 c. leaves	100
+12.0	4,000	120	250	1	60	21	2½ c. leaves	100
+	88	□	□	<1	6	155	1 tuber, pared	150
+15.0	100	80	□	□	x	110	1 corm, pared	100

COMPOSITION

(EDIBLE

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE OTHER THAN FIBER	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Apples	60	0.3	13.9	0.4	1.0	0.3	.007	.012	.00036	.00010
Apricots	54	1.0	12.3	0.1	0.6	0.6	.014	.025	.00061	.00018
Avocados	259	1.7	3.7	26.4	1.4	1.3	.010	.038	.00057	.00021
Bananas	96	1.2	22.4	0.2	0.6	0.8	.009	.031	.00064	.00021
Blackberries	46	1.2	7.8	1.1	4.1	0.5	.017	.030	.00091	.00016
Blueberries (huckleberries)	63	0.6	13.9	0.6	1.2	0.3	.025	.020	.00080	.00011
Cantaloupes	20	0.6	4.0	0.2	0.6	0.6	.017	.015	.00051	.00006
Cherries	67	1.1	14.5	0.5	0.3	0.6	.019	.031	.00040	.00014
Cranberries	48	0.4	9.9	0.7	1.4	0.2	.046	.020	.00044	.00009
Currants	48	1.6	9.5	0.4	3.2	0.6	.060	.036	.00063	.00110
Dates, dried	306	2.2	73.0	0.6	2.4	1.8	.065	.056	.00360	.00038
Figs, dried	277	4.0	62.6	1.2	5.8	2.4	.162	.116	.00290	.00035
Gooseberries	37	0.8	7.6	0.4	2.5	0.4	.040	.050	.00047	.00008
Grapefruit	43	0.5	9.8	0.2	0.3	0.4	.021	.020	.00027	.00003
Grapes	72	0.8	16.2	0.4	0.5	0.5	.017	.021	.00073	.00009
Guavas	56	1.0	11.6	0.6	5.5	0.7	.015	.016	.00030	.00002
Honeydew Melons	34	0.6	7.5	0.2	0.5	0.6	.017	.016	.00040	.00007
Lemons	40	0.9	7.8	0.6	0.9	0.5	.036	.022	.00060	.00004
Limes	52	0.8	12.0	0.1	0.3	0.6	.055	.036	.00060	.00097
Loganberries	64	1.0	13.6	0.6	1.4	0.5	.035	.024	.00140	.00014
Mangoes	69	0.7	16.2	0.2	1.0	0.5	.005	.016	.00030	.00001
Muskmelons	26	0.6	5.4	0.6	0.5	0.6	.016	.015	.00039	.00006
Nectarines	65	0.5	15.6	0.1	0.4	0.5	.004	.024	.00046	.00006
Olives, green	139	1.5	2.8	13.5	1.2	5.8	.122	.014	.00029	.00018
Oranges	48	0.9	10.6	0.2	0.6	0.5	.045	.021	.00052	.00008
Papayas	40	0.6	9.1	0.1	0.9	0.6	.019	.013	.00030	.00001
Peaches, yellow	49	0.5	11.4	0.1	0.6	0.5	.016	.024	.00035	.00009
Pears	64	0.7	14.4	0.4	1.4	0.4	.015	.026	.00035	.00010
Persimmons	135	0.8	32.0	0.4	1.5	0.9	.022	.021	.00027	-----
Pineapples	57	0.4	13.3	0.2	0.4	0.4	.018	.028	.00037	.00007
Plums	54	0.7	12.4	0.2	0.5	0.5	.020	.027	.00056	.00015
Pomegranates	74	0.6	17.4	0.2	0.3	0.5	.011	.105	.00078	.00007
Prunes, dried	292	2.3	69.4	0.6	1.6	2.1	.054	.105	.00290	.00041
Quinces	51	0.3	12.1	0.1	1.8	0.4	.014	.021	.00100	.00014
Raisins	292	2.3	69.5	0.5	1.7	2.0	.064	.132	.00430	.00020
Raspberries, black	69	1.5	12.1	1.6	3.5	0.7	.049	.052	.00088	.00014
Raspberries, red	56	1.1	11.6	0.6	2.8	0.5	.041	.035	.00088	.00013
Strawberries	36	0.8	6.9	0.6	1.2	0.5	.041	.028	.00068	.00002
Tangerines	46	0.8	9.9	0.3	1.0	0.7	.042	.017	.00061	.00009
Watermelons	29	0.5	6.3	0.2	0.6	0.3	.007	.012	.00023	.00007

[e] The ash of these foods is alkaline, but because of substances in them which form hippuric acid in the body, they increase the acidity of the urine.

[f] Ripe olives are soaked in alkali during their manufacture, and the alkaline content is apt to be high.

See pages 750 and 751 for other footnotes.

OF FRUITS
PORTION)

ALKALINE (+) OR ACID (-) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE	WEIGHT IN GRAMS
+ 3.7	50	45	50	0	6	90	1 large, cored	150
+ 6.1	4000	30	75	<1	11	54	4 halves, stoned	100
+11.0	290	120	150	1	16	259	½ pear, pared, stoned	100
+ 5.6	400	60	90	<1	28	96	1 small, peeled	100
+ 6.9	83	45	60	0	10	46	1 c.	100
+ 2.7	100	45	18	0	15	63	⅔ c.	100
+ 7.5	1000	50	75	1	42	40	½ seeded, rind removed	200
+ 4.5	200	50	40	0	12	67	18 stoned	100
– [e]	70	30	x	0	15	48	1 c.	100
+ 6.3	400	30	140	□	100	48	1 c.	100
+11.0	210	72	100	2	2	92	4 stoned	30
+33.0	75	100	100	2	2	83	1½	30
+ 3.3	380	150	□	□	25	37	⅔ c.	100
+ 7.0	20	72	40	0	42	43	½ c. juice	100
+ 4.0	50	45	40	< 1	5	72	1 bunch, seeded	100
+ 8.0	200	150	90	1	250	56	1 pared, seeded	100
----	50	46	□	0	21	68	⅙ seeded, rind removed	200
+ 5.0	20	60	5	0	46	40	½ c. juice	100
+10.0	130	60	5	0	36	52	½ c. juice	100
+ 7.3	x	33	□	□	35	64	1 c.	100
+ 5.0	1500	60	100	□	60	69	½ pared, seeded	100
+ 7.5	2400	57	75	1	25	52	½ seeded, rind removed	200
+ 6.2	2800	72	□	□	25	65	2 pared, stoned	100
+ [f]	420	8	x	0	0	35	5 small, stoned	25
+ 5.6	90	78	60	0	48	48	½ c. juice	100
----	3000	75	150	□	42	40	½ seeded, rind removed	100
+ 5.9	1700	20	64	1	8	49	1 large, pared, stoned	100
+ 4.2	15	40	76	0	5	64	2 halves, cored pared	100
----	2600	0	□	□	100	135	1 small, seeded	100
+ 6.8	200	90	55	0	38	57	2 slices, canned	100
– [e]	360	100	45	<1	5	54	3 stoned	100
+ 3.5	□	□	100	□	6	74	½ seeded	100
– [e]	1600	180	160	2	3	108	4 stewed, stoned	37
+ 4.9	□	□	□	□	9	51	1 boiled, as a sauce	100
+34.0	50	100	130	<1	3	131	⅓ c. seeded and seedless	45
+ 3.8	0	21	□	□	30	69	⅞ c.	100
+ 6.0	130	21	□	□	30	56	⅞ c.	100
+ 5.5	50	33	70	0	60	36	12 hulled	100
+ 5.3	300	120	40	0	48	46	2 peeled, seeded	100
+ 2.7	500	60	35	0	7	58	1 slice, seeded	200

COMPOSITION OF CEREALS
(EDIBLE

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE OTHER THAN FIBER	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Barley, pearled	355	8.2	78.3	1.0	0.5	0.9	.020	.181	.00200	.00040
Bread, enriched white	260	8.5	52.0	2.0	0.3	1.3	.180	.098	.00280	.00034
Bread, rye	250	8.9	49.2	2.0	0.5	1.8	.024	.148	.00160	.00028
Bread, white	260	8.5	52.0	2.0	0.3	1.3	.080	.098	.00090	.00034
Bread, whole wheat	258	9.5	47.0	3.5	1.0	2.0	.078	.262	.00300	.00050
Cake, devils food, iced	354	6.2	64.1	8.1	0.2	1.1	.122	.202	.00590	.00006
Cake, sponge	293	7.9	54.2	5.0	0.2	0.9	.073	.221	.00330	.00004
Cookies (average)	378	7.0	62.4	11.2	0.4	---	.050	.080	.00150	-----
Cornmeal, yellow	357	9.1	71.9	3.7	2.0	1.3	.018	.276	.00270	.00020
Crackers, Graham	416	8.0	73.5	10.0	0.8	2.2	.020	.203	.00190	-----
Crackers, soda	415	9.6	72.5	9.6	0.2	2.4	.022	.102	.00150	-----
Doughnuts	425	6.6	52.5	21.0	0.2	1.0	.045	.083	.00190	.00011
Farina	368	11.0	79.0	0.9	0.3	0.4	.021	.125	.00080	.00029
Farina, enriched	368	11.0	79.0	0.9	0.3	0.4	.504	.125	.00530	.00029
Flour, buckwheat	352	6.3	79.3	1.1	0.4	0.9	.010	.176	.00120	.00070
Flour, rye	353	8.9	77.4	0.9	1.1	0.7	.018	.289	00130	.00042
Flour, soybean	458	40.5	24.5	22.0	2.5	5.0	.280	.600	.01200	.00120
Flour, white	354	10.8	75.6	0.9	0.3	0.4	.020	.092	.00078	.00017
Flour, enriched min.	---	---	---	---	---	---	.110	---	.00290	-----
Flour, enriched max	---	---	---	---	---	---	.140	---	.00360	-----
Flour, whole wheat	356	13.0	71.5	2.0	0.9	1.6	.038	.385	.00380	-----
Hominy, white	355	8.5	78.5	0.8	0.4	0.4	.011	.144	.00090	.00019
Macaroni, Spaghetti	359	13.0	73.5	1.4	0.4	0.7	.022	.144	.00120	.00007
Noodles, egg	382	14.3	70.0	5.0	0.6	0.7	.024	.156	.00190	-----
Oatmeal (Rolled Oats)	391	14.2	67.0	7.4	1.2	1.9	.069	.392	.00380	.00050
Popcorn, popped	405	10.7	78.7	5.3	1.7	1.5	.020	---	.00190	-----
Pretzels	361	8.8	74.2	3.2	0.3	5.5	.037	.130	.00130	-----
Rice, brown	354	7.5	77.1	1.7	0.6	1.1	.039	.303	.00550	.00036
Rice, white	350	7.6	79.2	0.3	0.2	0.4	.009	.096	.00090	.00019
Tapioca	349	0.6	86.3	0.2	0.1	0.2	.012	.012	.00160	.00007
Wheat bran	312	16.0	50.2	5.2	17.1	4.9	.120	1.215	.01260	.00120
Wheat germ	379	25.2	47.0	10.0	2.5	4.3	.070	1.050	.00860	.00130
Wheat, whole	361	11.7	74.0	2.0	1.8	1.8	.045	.423	.00430	.00060

See pages 750, 751, and 754 for footnotes.

AND BAKERY PRODUCTS
PORTION)

ALKALINE (+) OR ACID (−) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B_1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE	WEIGHT IN GRAMS
-10.0	0	120	60	3	0	107	3 T.	30
- 4.0	0	400	350	3	0	130	2 slices	50
- 5.2	0	210	40	1	0	125	3 slices	50
- 4.0	0	90	90	1	0	130	2 slices	50
- 3.6	20	300	140	4	0	129	2 slices	50
- 6.3	300	40	120	1	0	202	1 piece	57
- 9.7	640	55	150	1	0	108	1 piece	37
- or +	250	90	80	3	0	106	1-2	28
- 4.9	510	450	170	2	0	107	3 T.	30
- 8.5	0	300	120	2	0	125	3	30
- 9.0	0	100	30	<1	0	104	4	25
- 1.7	190	280	220	2	0	242	1	57
-11.0	0	50	60	1	0	110	3 T.	30
-11.0	0	530	270	3	0	110	3 T.	30
- 7.1	0	300	80	2	0	77	2 T.	22
-11.0	0	180	60	1	0	64	2 T.	18
+ 9.5	140	540	410	2	0	82	2 T.	18
- 9.0	0	87	40	1	0	60	2 T.	17
----	----	440	260	3.5	--	---		---
----	----	550	330	4.4	--	---		---
-11.0	25	500	120	6	0	57	2 T.	16
- 1.7	0	180	60	1	0	178	¼ c.	50
-14.0	0	130	70	2	0	101	¼ c.	28
-	180	180	110	2	0	382	¾ c.	100
-12.0	0	810	150	1	0	98	¼ c.	25
- 8.0	500	x	x	1	0	69	1 c.	17
- 7.0	0	0	0	□	0	90	6	25
- 5.7	20	300	60	5	0	106	3 T.	30
- 9.0	0	40	20	1	0	98	2 T.	28
0.0	0	0	100	0	0	140	¼ c.	40
-25.0	140	520	350	32	0	87	1 c.	28
-20.0	100	3500	700	7	0	76	2 T.	20
-12.0	14	520	120	6	0	72	2 T.	20

COMPOSITION OF MEATS, FISH,
(EDIBLE

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Bacon (lean)	531	12.2	1.4	53.0	---	4.7	.006	.108	.00240	.00050
Beef brains	127	10.5	1.4	8.8	---	1.4	.016	.340	.00530	.00021
Beef, chuck (good grade)	268	17.6	0.0	22.0	---	0.8	.012	.220	.00300	.00010
Beef, chuck (common grade)	---	19.2	0.0	9.0	---	0.9	---	---	-----	-----
Beef, corned (medium)	288	15.8	0.0	25.0	---	5.0	.009	.170	.00240	-----
Beef, corned (very lean)	---	19.4	0.0	8.0	---	6.2	---	---	-----	-----
Beef heart (lean)	104	16.9	0.7	3.7	---	1.1	.018	.268	.00350	.00000
Beef kidney	137	15.0	0.9	8.1	---	1.1	.009	.182	.00410	.00011
Beef liver	132	19.7	6.0	3.2	---	1.4	.008	.420	.00790	.00220
Beef, loin (good grade)	341	15.6	0.0	31.0	---	0.8	.012	.216	.00300	.00010
Beef, loin (common grade)	---	18.6	0.0	16.0	---	1.0	---	---	-----	-----
Beef steak (good grade)	233	18.7	1.4	17.0	---	0.9	.012	.216	.00300	.00010
Beef steak (common grade)	---	19.7	0.0	8.0	---	1.0	---	---	-----	-----
Beef sweetbreads (good grade)	410	10.3	0.0	41.0	---	0.9	.014	.595	.00160	.00008
Beef sweetbreads (common grade)	---	14.4	0.0	19.0	---	1.5	---	---	-----	-----
Beef tongue (good grade)	226	15.7	0.4	18.0	---	0.8	.008	.200	.00600	-----
Beef tongue (common grade)	---	17.4	0.4	11.0	---	0.9	---	---	-----	-----
Bluefish	118	20.5	0.0	4.0	---	1.2	.023	.236	.00060	.00023
Bologna	217	14.8	3.6	15.9	---	3.0	.009	.160	.00220	.00000
Chicken	125	21.1	0.0	4.5	---	1.1	.012	.232	.00320	.00035
Clams	77	12.8	3.4	1.4	---	2.1	.109	.099	.00430	-----
Codfish	70	16.5	0.0	0.4	---	1.2	.018	.189	.00090	.00055
Crabs	81	16.1	0.6	1.6	---	1.7	.017	.181	.00610	.00057
Duck	159	21.4	0.0	8.2	---	1.2	.010	.200	.00230	.00050
Egg whites	46	10.8	0.8	0.0	---	0.6	.015	.014	.00010	.00007
Egg yolks	355	16.3	0.7	31.9	---	1.7	.147	.586	.00860	.00040
Eggs	158	12.8	0.7	11.5	---	1.6	.054	.210	.00300	.00023
Frankfurters	201	15.2	3.3	14.1	---	2.8	.009	.164	.00230	-----
Gelatin, dried	343	85.6	0.0	0.1	---	1.3	.453	.234	-----	-----
Goose	153	22.3	0.0	7.1	---	1.1	.009	.175	.00240	.00033
Haddock	72	17.2	0.0	0.3	---	1.2	.018	.197	.00050	.00028
Halibut	121	18.6	0.0	5.2	---	1.0	.020	.200	.00100	.00023
Ham (fat)	456	14.6	0.3	44.0	---	5.1	.012	.215	.00300	-----

See pages 750, 751, and 754 for footnotes.

AND POULTRY PRODUCTS
PORTION)

ALKALINE (+) OR ACID (−) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B_1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE	WEIGHT IN GRAMS
- 4.8	0	270	150	2	0	149	4 slices	28
-21.0	54	170	300	5	19	144	¼ lb.	113
-11.0	21	84	270	5	0	303	¼ lb.	113
----	----	---	---	--	--	---		---
-10.0	40	87	100	2	0	325	¼ lb.	113
----	----	---	---	--	--	---		---
- 9.1	200	660	750	6	4	118	¼ lb.	113
- 8.5	1,100	400	2000	10	11	155	1 c.	113
- 11.0	20,000	270	2500	20	41	149	¼ lb.	113
- 11.0	21	210	350	6	2	385	¼ lb.	113
----	----	---	--	--	--	---		---
-11.0	21	210	350	6	2	263	¼ lb.	113
----	----	---	---	--	--	---		---
- 12.0	x	330	670	3	20	463	1 c.	113
----	----	---	---	--	--	---		---
-11.0	0	280	220	13	0	170	5 slices	75
----	----	---	---	--	--	---		---
- 9.0	0	x	200	□	0	133	1 fish filet	113
- 8.5	0	310	300	3	0	93	4 slices, skin removed	43
-14.0	x	120	170	7	4	141	¼ lb.	113
--	200	20	120	1	30	87	9	113
- 8.4	10	40	50	2	2	79	¼ lb. filet	113
-40.0	xx	140	350	3	13	92	⅔ c.	113
-24.0	xx	360	230	3	8	180	¼ lb.	113
- 5.2	0	0	250	0	0	16	1 white	35
-27.0	2,800	420	400	0	0	60	1 yolk	17
-11.0	1,000	150	300	0	0	82	1, shell removed	52
- 9.3	0	190	230	3	0	227	2 links	113
-	0	0	0	0	0	31	1 T.	9
- 7.8	□	150	xx	3	13	173	¼ lb.	113
-12.0	7	120	160	1	0	81	¼ lb. filet	113
- 9.3	6	120	180	6	0	137	¼ lb. filet	113
- 9.5	0	1400	250	6	0	515	¼ lb.	113

COMPOSITION OF MEATS, FISH,
(EDIBLE

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE	FAT	CRUDF FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Ham (lean)	---	19.5	0.3	25.0	---	5.8	---	---	-----	-----
Herring	136	19.0	0.0	6.7	---	1.6	.021	.224	.00060	.00028
Lamb chops	230	18.0	0.0	17.5	---	1.3	.010	.194	.00270	.00042
Lamb, leg	230	18.0	0.0	17.5	---	1.2	.010	.194	.00270	.00040
Lobster	84	16.2	0.5	1.9	---	2.2	.018	.188	.00090	.00070
Mackerel	183	18.7	0.0	12.0	---	1.2	.011	.273	.00100	.00030
Margarine, fortified	733	0.6	0.4	81.0	---	2.5	.004	.012	.00030	.00004
Mince meat	280	6.7	60.2	1.4	---	4.0	.085	.175	.00300	.00008
Oysters	81	9.8	5.9	2.0	---	2.0	.052	.155	.00450	.00300
Pork chops (good grade)	347	14.8	0.0	32.0	---	0.8	.010	.180	.00250	.00031
Pork chops (common grade)	---	17.9	0.0	18.0	---	1.0	---	---	-----	-----
Pork sausage	446	10.8	0.0	44.8	---	2.1	.007	.116	.00160	.00012
Rabbit	175	20.8	0.0	10.2	---	1.1	.019	.183	.00056	.00020
Salmon	218	17.4	0.0	16.5	---	1.0	.025	.250	.00120	.00020
Sardines in oil	207	25.7	1.2	11.0	---	4.7	.340	.390	.00200	.00004
Scallops	74	14.8	3.4	0.1	---	1.4	.115	.338	.00300	.00023
Shrimp	111	25.4	0.2	1.0	---	2.6	.096	.292	.00270	.00043
Tripe	94	19.1	0.0	2.0	---	0.4	.127	.132	.00160	-----
Tuna in oil	194	24.2	0.0	10.8	---	2.0	.030	.300	.00150	.00050
Turkey	156	24.0	0.0	6.7	---	1.1	.030	.420	.00450	.00018
Veal chops (good grade)	209	18.6	0.0	15.0	---	1.0	.012	.220	.00300	.00025
Veal chops (common grade)	---	19.7	0.0	8.0	---	1.0	---	---	.00300	-----
Veal cutlet (good grade)	184	19.1	0.0	12.0	---	1.0	0.15	.228	-----	.00025
Veal cutlet (common grade)	---	19.9	0.0	6.0	---	1.1	---	---		-----
Whitefish	150	22.9	0.0	6.5	---	1.6	.025	.263	.00042	.00019

See pages 750, 751, and 754 for footnotes.

AND POULTRY PRODUCTS
PORTION)

ALKALINE (+) OR ACID (−) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B_1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE	WEIGHT IN GRAMS
----	----	---	---	--	--	---		---
-9.0	200	120	310	4	0	154	1 filet	113
-9.7	0	210	260	6	0	260	2 chops	113
-9.6	0	210	260	6	3	260	¼ lb.	113
-38.0	□	150	130	□	5	95	⅔ c. canned	113
-11.0	150	120	660	6	0	207	1 filet	113
0.0	2,000	6	0	0	0	103	1 T.	14
+12.0	□	□	□	□	0	316	¼ lb.	113
-23.0	210	200	460	1	3	92	6	113
-8.0	x	1400	240	7	2	392	2 chops	113
----	----	---	---	--	--	---		---
-7.5	0	220	150	2	0	156	2 links	35
-15.0	0	90	60	7	4	198	¼ lb.	113
-11.0	270	120	220	7	9	246	1 c. canned	113
-11.0	140	90	350	4	0	104	4 sardines	50
-36.0	180	xx	x	1	3	84	⅔ c.	113
-1.6	60	90	160	1	3	72	8	65
-8.1	□	6	120	3	□	106	¼ lb.	113
-	200	50	200	10	0	111	½ c., canned	57
-11.0	x	150	240	7	0	176	¼ lb.	113
-14.0	35	270	240	7	0	236	2 chops	113
----	----	---	---	--	--	---		---
-9.8	30	120	300	8	0	208	¼ lb.	113
----	----	---	---	--	--	---		---
-10.0	12	90	xx	□	0	170	¼ lb. filet	113

COMPOSITION
(EDIBLE

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE OTHER THAN FIBER	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Almonds	629	18.6	16.9	54.1	2.7	3.0	.254	.475	.00400	.00120
Brazil nuts	686	14.4	8.9	65.9	2.1	3.4	.176	.592	.00400	.00140
Butternuts	679	23.7	8.4	61.2	---	2.9	---	---	.00680	.00120
Cashew	605	19.6	25.4	47.2	1.0	2.7	.048	.480	-----	-----
Chestnuts, fresh	186	2.8	40.4	1.5	1.1	1.0	.034	.093	.00410	.00060
Coconut, dried	566	3.6	49.8	39.1	3.4	1.3	.043	.191	.00360	.00069
Hazelnuts (filberts)	656	12.7	14.3	60.9	3.4	2.7	.287	.354	.00410	.00120
Hickory	706	13.9	11.0	67.4	2.2	2.0	---	---	.00290	.00140
Peanuts	590	26.9	21.2	44.2	2.4	2.7	.071	.399	.00200	.00100
Peanut butter	611	26.1	19.0	47.8	2.0	3.4	.072	.396	.00180	.00055
Pecans	738	94	10.8	73.0	2.2	1.6	.089	.335	.00260	.00140
Pistachios	623	19.6	16.4	53.2	2.2	3.0	---	---	.00790	.00120
Walnuts, black	664	18.3	16.8	58.2	1.9	2.1	---	---	.00600	.00320
Walnuts, English	694	15.0	13.5	64.4	2.1	1.7	.060	.360	.00210	.00100

COMPOSITION

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE OTHER THAN FIBER	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Apple Juice	50	0.1	12.5	0.0	0.0	---	.006	.010	.00029	.00008
Cocoa, with milk	117	4.9	11.9	5.5	0.2	---	.143	.132	.00043	.00016
Coffee, black[g]	4	0.2	0.7	0.0	---	---	.004	.004	.00046	-----
Cola[g]	41	---	10.3	---	---	---	---	.017	-----	-----
Ginger Ale[g]	36	---	9.0	---	---	---	---	---	-----	-----
Grape Juice	76	0.3	18.6	0.0	0.0	0.4	.010	.010	.00030	.00002
Grapefruit Juice	42	0.4	9.8	0.1	0.3	0.4	.010	.017	.00027	-----
Lemonade, plain	42	0.0	10.5	0.0	---	---	.003	.001	.00070	.00013
Orange Juice	45	0.7	10.1	0.2	0.0	0.4	.011	.015	.00031	.00008
Pineapple Juice	54	0.3	13.0	0.1	0.4	0.4	.016	.013	.00040	-----
Prune Juice	79	0.4	19.3	0.0	0.0	---	.010	.020	.00076	-----
Raspberry Juice	35	0.4	8.3	0.0	0.0	---	.024	.012	.00080	-----
Root Beer[g]	32	---	8.0	---	---	---	---	---	-----	-----
Sauerkraut Juice	3	0.0	0.7	0.0	---	---	.000	.000	.00000	.00000
Soda Pop[g]	48	---	12.0	---	---	---	---	.017	-----	-----
Tea, black[g]	---	---	---	---	---	---	.001	.001	.00072	-----
Tomato Juice	23	0.9	4.4	0.2	0.2	1.0	.007	.015	.00050	.00005

[g] Except as shown the analysis, vitamin, and mineral content are practically nil.

See page 766, for analytical figures of cocoa, dried coffee bean, and dried tea leaves. See pages 750, 751, and 754 for other footnotes.

OF NUTS
PORTION)

ALKALINE (+) OR ACID (-) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B_1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE	WEIGHT IN GRAMS
+12.0	0	300	600	5	0	88	12 nuts	14
+ 4.5	10	1100	70	□	0	96	2 nuts	14
----	x	xx	□	□	0	95	4 nuts	14
----	x	150	190	□	0	85	10 nuts	14
+ 5.0	80	240	x	1	6	26	3 nuts, skin removed	14
+ 8.3	0	70	100	<1	0	79	2 T.	14
+ 4.8	440	500	xx	□	0	92	10 nuts	14
----	□	600	xx	□	0	99	12 nuts	14
- 3.9	360	400	500	16	0	83	16 nuts, skin removed	14
- 3.9	360	300	320	16	0	104	1 T.	17
- 5.6	400	1000	250	1	0	103	12 meats	14
----	200	□	□	□	0	87	⅛ c.	14
-	130	330	□	□	0	93	12 meats	14
- 7.8	40	340	280	1	0	97	12 meats	14

OF BEVERAGES

ALKALINE (+) OR ACID (-) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B_1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE[e]	WEIGHT IN GRAMS
+	36	20	30	0	3	60	1 small glass	120
+ 2.2	420	75	230	0	0.9	211	1 c.	180
----	----	---	---	<1	--	7	1 c.	180
----	----	---	---	--	--	70	1 bottle	170
----	----	---	---	--	--	61	1 bottle	170
+ 3.9	0	30	30	0	6	91	1 small glass	120
+ 3.2	21	50	30	0	41	50	1 small glass	120
+ 0.5	□	8	10	0	5	88	1 glass	210
+ 5.6	250	60	60	0	35	54	1 small glass	120
+ 3.8	90	70	20	0	25	65	1 small glass	120
- [e]	1,200	50	□	<1	5	95	1 small glass	120
+ 6.2	100	20	□	□	20	42	1 small glass	120
----	----	---	---	--	--	54	1 bottle	170
+	0	110	50	□	8	4	1 small glass	120
----	----	---	---	--	--	82	1 bottle	170
----	----	---	---	<1	--	---	1 c.	180
+ 5.3	1,200	80	45	<1	20	28	1 small glass	120

COMPOSITION OF

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Butter	733	0.6	0.4	81.0	---	2.5	.015	.017	.00020	h
Buttermilk	35	3.5	5.1	0.1	---	0.8	.118	.093	.00025	.00005
Cheese, American	393	23.9	1.7	32.3	---	3.1	.930	.683	.00140	.00018
Cheese, Cheddar	393	23.9	1.7	32.3	---	5.8	.873	.610	.00130	.00005
Cheese, Cottage	101	19.2	4.3	0.8	---	1.2	.082	.263	.00046	-----
Cheese, Cream	367	7.1	1.7	36.9	---	1.0	.635	.528	.00130	.00004
Cheese, Roquefort	391	21.7	1.4	33.2	---	6.3	.721	.525	.00098	-----
Cheese, Swiss	404	28.6	1.9	31.3	---	4.2	1.050	.845	.00130	.00013
Cream, sour	195	2.5	4.5	18.5	---	0.5	.090	.080	.00022	.00015
Cream, sweet	208	2.9	4.0	20.0	---	0.6	.090 .150	.080	.00022	.00015
Ice Cream, Vanilla	214	3.9	20.3	13.0	---	0.8	.122	.120	.00036	.00003
Milk, chocolate	83	2.2	15.6	1.3	---	---		.096	.00020	.00003
Milk, condensed (sweetened)	327	8.1	54.8	8.4	---	1.7	.273	.228	.00060	.00010
Milk, dried skim (Defatted milk solids)	359	36.8	50.9	0.9	---	8.2	1.315 .960	1.020	.00350	.00057
Milk, dried whole	503	26.5	38.4	27.0	---	6.1	.090	.720	.00064	.00016
Milk, evaporated	139	7.0	9.9	7.9	---	1.5	.250	.200	.00053	.00012
Milk, goat	70	3.3	4.8	4.2	---	0.7	.128	.103	.00020	.00002
Milk, human	68	1.4	7.2	3.7	---	0.2	.034	.015	.00018	.00006
Milk, skim	36	3.5	5.0	0.2	---	0.8	.122	.096	.00025	.00002
Milk, whole (pasteurized)	69	3.5	4.9	3.9	---	0.7	.120	.093	.00024	.00002
Whey, dried	355	13.0	74.5	0.5	---	8.5	.572	.524	.00070	-----

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[h] Dependent on type of container in which it is processed.

See pages 750, 751, and 754 for other footnotes.

PRODUCTS

Alkaline (+) or Acid (−) Effect[b]	Vitamin Content per 100 Grams, see footnote[c]					Average Portion		
	A	B1	B2	Nicotinic Acid	C	Total Calories	Measure	Weight in Grams
0.0	2,400	0-120	37	0	0	103	2 pats	14
+ 2.2	25	42	180	0	1.5	74	1 glass	210
- 5.4	2,000	42	450	0	0	110	1 slice	28
- 5.0	2,000	42	600	0	0	110	1 cube	28
- 4.5	110	20	300	0	0	28	⅛ c.	28
- 3.4	2,200	30	150	0	0.9	104	1 cube	28
+	4,000	30	450	1	0	109	1 slice	28
- 5.0	2,700	30	370	<1	0	113	1 slice	28
-	2,200	60	350	0	1.0	29	1 T.	15
0.0	1,600	60	350	0	1.0	31	1 T.	15
+ 0.2	900	24	150	0	1.0	214	½ c.	100
+ 1.5	20	40	180	0	0.8	174	1 glass	210
+ 5.2	280	72	350	0	1.0	98	2 T.	30
+18.0	140	360	2100	1	7.0	57	2 T.	16
+12.0	1,400	300	1500	1	6.0	80	2 T.	16
+ 5.1	460	60	320	0	1.5	139	½ glass	100
+	170	60	80	0	1.5	147	1 glass	210
+	350	14	37	0	6.0	68		100
+ 2.4	17	42	160	0	1.4	76	1 glass	210
+ 2.3	170	36	170	0	0.7	145	1 glass	210
+	☐	1100	5900	<15	0	28	1 T.	8

COMPOSITION OF
(Edible

NAME	CALORIES PER 100 GRAMS	PERCENTAGE BY WEIGHT								
		PROTEIN	CARBOHYDRATE OTHER THAN FIBER	FAT	CRUDE FIBER	ASH	CALCIUM	PHOSPHORUS	IRON	COPPER
Apple Pie	216	1.6	32.0	9.1	0.6	1.8	.011	.021	.00190	-----
Candy (average)	503	9.2	59.5	25.3	0.0	---	.080	.180	.00250	-----
Chocolate, milk	541	6.0	61.8	30.0	0.3	1.4	.196	.200	.00100	.00007
Chocolate, sweetened	549	3.8	61.5	32.0	0.9	1.1	.032	.154	.00240	.00090
Chocolate, unsweetened	631	11.0	27.4	53.0	2.8	2.8	.093	.447	.00690	.00250
Cocoa (Breakfast)	453	17.5	44.0	23.0	4.4	4.4	.149	.715	.01090	.00400
Cocoa (medium-fat)	407	19.3	48.8	15.0	4.9	5.0	.163	.785	.01210	.00440
Cod-liver oil	900	0.0	0.0	100.0	0.0	0.0	---	---	-----	.00001
Coffee[1]	308	17.2	22.7	16.5	18.4	4.9	.133	.161	.00670	.00180
Corn oil	900	0.0	0.0	100.0	0.0	0.0	.000	.000	.00000	.00000
Corn syrup	297	0.2	74.0	0.0	0.0	0.6	.010	.007	.00150	.00009
Cottonseed oil	900	0.0	0.0	100.0	0.0	0.0	.000	.000	.00000	.00000
Honey	319	0.3	79.5	0.0	0.0	0.2	.004	.019	.00070	.00020
Ketchup, tomato	108	2.0	24.1	0.4	0.4	3.6	.017	.042	.00120	.00130
Lard	900	0.0	0.0	100.0	0.0	0.0	.000	.000	.00000	.00000
Maple syrup	256	0.0	64.0	0.0	0.0	0.7	.107	.013	.00300	-----
Marmalade, orange	341	0.6	84.5	0.1	0.0	0.5	.035	.013	.00058	.00012
Molasses	286	2.1	69.3	0.0	0.0	3.2	.211	.044	.00730	.00190
Olive oil	900	0.0	0.0	100.0	0.0	0.0	.001	.000	.00008	.00007
Pickles	85	0.4	20.7	0.1	0.4	1.7	.009	.008	.00120	.00021
Potato Chips	571	6.7	46.7	39.7	1.3	4.0	.040	.100	.00330	-----
Succotash	94	3.6	17.7	1.0	0.9	0.9	---	---	-----	-----
Sugar										
Granulated (sucrose)	398	0.0	99.5	0.0	0.0	0.0	.000	.000	.00000	.00000
Brown	384	0.4	95.5	0.0	0.0	1.2	.090	.012	.00260	-----
Tea[1]	249	24.1	19.7	8.2	10.6	5.9	.426	.628	.01550	.00160
Yeast, fresh	108	13.3	12.7	0.4	0.3	2.4	.025	.605	.00490	-----
Yeast, dried brewers	345	46.1	36.6	1.6	0.8	7.9	.106	1.890	.01820	.00200

Chemically there is no difference between cane and beet sugars. They also have similar physical properties and have equal nutritive value.

See pages 750, 751, and 754 for other footnotes.

MISCELLANEOUS FOODS

PORTION)

ALKALINE (+) OR ACID (−) EFFECT[b]	VITAMIN CONTENT PER 100 GRAMS, SEE FOOTNOTE[c]					AVERAGE PORTION		
	A	B_1	B2	NICOTINIC ACID	C	TOTAL CALORIES	MEASURE	WEIGHT IN GRAMS
+ 3.0	42	27	32	0	4	346	1 piece, ⅙ pie	160
− or +	200	80	140	4	0	287		57
+ 2.9	480	50	290	□	0	308	1 bar	57
+ 2.4	36	14	□	□	0	313		57
+ 6.7	60	42	240	1	0	32	1 T.	5
+11.0	26	67	390	2	0	27	2 t.	6
+12.0	17	75	390	2	0	24	2 t.	6
0.0	85,000	0	0	0	0	99	1 T.	11
+63.0	900	900	70	10	0	---	1 c. infusion	180
0.0	0	0	0	□	0	99	1 T.	11
0.0	0	0	10	0	0	65	1 T.	22
0.0	0	0	0	0	0	99	1 T.	11
− 1.1	0	6	60	0	5	80	1 T.	25
+	270	120	70	2	11	22	1 T.	20
0.0	0	0-100	10	0	0	126	1 T.	14
+	0	0	0	□	0	56	1 T.	22
+ 2.8	5	20	20	0	7	85	1 T.	25
+60.0	0	50	160	4	0	40	2 t.	14
0.0	20	0	0	□	0	99	1 T.	11
−	190	10	30	0	7	24	4 small	28
+21.0	80	350	210	1	15	97	8-10 large pieces	17
+	400	90	100	□	8	94	⅓ c.	100
0.0	0	0	0	0	0	32	2 t.	8
+60.0	0	0	0	0	0	19	2 t.	5
+47.0	0	0	350	7	0	---	1 c. infusion	180
----	0	3,500	1500	10	0	15	1 cake	14
+17.0	0	14,000	5000	50	0	35	1 T.	10

---

[1] The infusion has little food value except for added sugar and cream. See page 762. The analytical figures apply to dried coffee bean and dried tea leaves.

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